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BULLETIN
OF
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HAEMORRHAGIC BRIGHT'S DISEASE[1]

I. Natural History

THOMAS ADDIS

From the Medical Department of Stanford University Medical School, San Francisco

Those who are responsible for the choice of the Thayer lecturers may have been influenced by a sense that it would be in keeping with the character of the man in whose honor they are given that the privilege should be allotted in successive years to men from widely diverse communities. For though we all know Dr. Thayer first of all as a personality, marked by strongly individual characteristics, yet even those who have the least and the most indirect acquaintance with him are very sure that his capacity for appreciation is all-embracing and truly catholic. So after the ancient medical tradition of England and an already complex and beautifully articulated spirit of investigation from the East coast of this country have spoken, it is surely appropriate that the far West also, a country where as yet there is little of tradition and where medical investigation is still relatively young and simple, should in its turn be allowed to pay its homage to Dr. Thayer.

It is, I suppose, characteristic of the immaturity of the West, that up to the last moment the very title of these lectures should have been in doubt. But on the whole there are good reasons for the avoidance of "glomerular nephritis," which says at once too little and too much, and for the use of the term Haemorrhagic Bright's disease, which at least commits us to no particular doctrine. But, whatever we choose to call it, this disease is still one of those interesting subjects of which we know so little that it is possible for us to go on talking about it almost interminably. There is nothing here of the discussion-destroying finality of mathematics. Even in comparison with other medical subjects the free expression of individual opinion is less hampered

[1] Delivered before the Johns Hopkins Medical Society as the Thayer Lecture in Clinical Medicine on May 11, 1931.

than on such matters as tuberculosis or malaria, where some limit is set by a general agreement about the tubercle bacillus and the malarial parasite. But here there is as yet no such hindrance and, as a consequence of this freedom, it may easily happen that what one of us says about this ill-defined disease may have no bearing on the remarks of another, simply because we are really not talking about the same thing at all. In such cases, of course, discussion is fruitless as well as endless.

There are two main currents of talk, the talk of the clinicians and the talk of the pathologists. Ostensibly they deal with different aspects of the same subject matter and ideally should fulfill one another and reach at last the same end. In fact, however, they tend to flow separately and endlessly on and never merge. One reason for this lack of any final unison is suggested by a comparison of the Haemorrhagic Bright's disease recognised by the clinician with the conception of the disease entertained by the pathologist. For although neither side can muster sufficient agreement within their own ranks to permit of anything which can be said to approximate the precision of a clinical or pathological definition, yet there is a certain combination of circumstances which unites all clinicians in the perception that here unquestionably they are dealing with Haemorrhagic Bright's disease, just as there are certain histological features so pure and uncomplicated as to still all discussion between pathologists.

The clinician's Haemorrhagic Bright's disease is a disease within a disease. A patient has scarlet fever or tonsillitis, and while he is yet in the stage of convalescense, his urine becomes bloody, his face swollen and he developes a mild hypertension. Haematuria is a symptom which is common to many different diseases, but it is only in the initial stage of Haemorrhagic Bright's disease that red blood cells, white blood cells, epithelial cells, casts, and a sufficient concentration of hematin-producing H ions, combine to produce the quite unmistakable coffee-like urine. Even when we do not see it, the spontaneous and unstudied description of the patient may suffice to bring it again before us. Hypertension is found in many unrelated diseases, but where else than at the beginning of Haemorrhagic Bright's disease do we find curves of systolic and diastolic pressure which day by day so smoothly and rapidly descend toward normal levels?

Edema, also, is in itself of no decisive diagnostic value, but it is only in the initial stage of Haemorrhagic Bright's disease that we find just that particular elastic non-pitting fulness of the skin of the whole body. The clinician's certainty of recognition is based on the unique combination of three signs, each one of which is in itself unique. He has ample justification for his conviction. He requires no confirmation from any other discipline than his own.

But the pathologist is not confronted with this, the clinician's, Haemorrhagic Bright's disease. The pathognomonic signs fade away; at last even the routine urine examinations return only doubtfully abnormal results, and in the end the patient escapes not only from the pathologist but even from the clinician.

The unfortunate clinician has to bring to the autopsy table for the pathologist's judgment just the type of patient in regard to whose diagnosis he feels most insecure. As a rule, the patient who dies in the wards of a University Hospital has had to struggle hard for a living. To him illness is a disaster, not an excuse, and he has shouldered out of his way and out of his memory those minor interruptions to health which others cherish. So he tells us that he has always been well and strong until at last he was forced to admit a progressive weakness, an unexplained and symptomless vomiting, a sudden blurring of vision or an increasing dyspnoea on exertion. The clinician now finds evidence of an embarrassing multiplicity of lesions, arterial, cardiac and renal. And when the patient comes to die of cerebral haemorrhage or thrombosis, of cardiac failure or of uraemia and the clinician is required to tell the pathologist what type of renal lesion will be found, there is not often any great confidence in the answer. The pathologist has learnt not to expect very much, but he would like to know from the clinician's study of the patient during life which of the various lesions the clinician supposed might be primary and predominant. The clinician tells him that the patient was arteriosclerotic and had albumin and casts in his urine and a very low 'phthalein excretion. His diagnosis is arteriosclerosis and nephritis. But the pathologist wants to know whether the patient became arteriosclerotic because he had had a nephritis, or whether he developed an albuminuria because he was arteriosclerotic. He really wants to know the answer to questions of that sort, because it would

help him in his interpretation of the histology of the kidney. And when, instead of answering such questions, the clinician recites the results of many elaborate chemical and physical measurements which demonstrate varying degrees of abnormality in renal function, the pathologist may be forgiven for growing impatient. He agrees there was something wrong with the way the kidneys worked, but the only thing that matters now is what sort of lesion is predominant in these kidneys. Low 'phthalein excretions, and high concentrations of urea in the blood may be found with all sorts of renal lesions or even with no renal lesion at all. And so the pathologist listens as politely as he can, but he goes unhelped to a study of the histology of the kidney. He has laboriously reconstructed the evolution of various types of renal lesion, and even though there is for him also a multiplicity of lesions, yet when he finds a certain amount and kind of inflammatory reaction in the glomeruli he reaches his own independent certainty. In that case his entirely justified attitude is "Here is the glomerulitis. This is what I call glomerular nephritis. If all these new tests and measurements of the clinician fail to lead him to a correct diagnosis, why, so much the worse for his observations." And yet the clinician has also had his moment of certainty, and if he had chanced to see this patient twenty years before when he had had the long forgotten or unobserved haematuria, hypertension and edema, and a pathologist had told him that this was not Haemorrhagic Bright's disease because there was no glomerulitis, the clinician would have been quite unperturbed. He would have replied that he did not care particularly what the pathologist called it, but his experience showed him that this was a quite unique clinical entity, characterised, in part, by bleeding from the kidney, cast formation and desquamation of renal cells. This was what he chose to call Haemorrhagic Bright's disease, and if the pathologist confessed that his histological investigations failed to account for these phenomena, why so much the worse for histology.

We have then a clear and confident beginning. And as a matter of fact, when, as rarely happens, clinician and pathologist meet over a patient in this initial stage there is a complete and happy unanimity. Histology confirms and makes more concrete the clinical certainty, and the clinician's data add significance to the interpretation of the

histological abnormalities. But that is only for a moment, for these symptoms fade, and these patients disappear. Their place is taken by others who are reaching an end which is complicated and obscure, an end which has no observed or remembered beginning and which in its main clinical features may quite possibly be produced not by Haemorrhagic Bright's disease but by such diverse conditions as amyloidosis or renal arteriosclerosis. And then it is the clinician who is in doubt; it is the pathologist who is relatively sure.

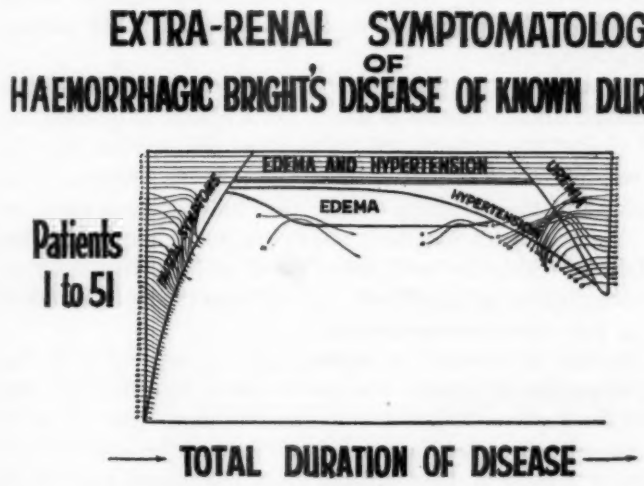

FIG. 1

Sometimes, of course, the clinician is more fortunate and has an opportunity to keep in touch with the patients who have passed through that unmistakable beginning. Or even if he himself did not observe the initial stage of the disease, the patient's recollections of his symptoms and of the diagnosis made at that time by his physician may suffice to establish with reasonable certainty the occurrence and date of the pathognomonic symptoms. Such a group may be followed until the renal lesion has come to its full fruition and has led to the patient's death in uraemia, or has so entirely healed that quantitative sediment counts yield results which are well within the limits of

normal variation. The whole clinical course of at least this group of patients may then be reconstructed.

Figure 1 attempts to portray observations made while such a group of patients were really patients in the sense of having something to complain about. There is the initial stage with its three cardinal signs, there is the end in uraemia, and in between there are spaces which are intended to designate that part of the course of the disease in which symptoms referable to arteriosclerosis and hypertension and to edema were observed. Only those conditions are depicted which are such as might bring a patient to consult a doctor. Each patient is represented by a line.

The diagram indicates that by far the greater part of its course Haemorrhagic Bright's disease is simply not a disease at all from the point of view of the patient. Of the fifty-one who started, only six remain constantly within clinical view. One or two reappear for a time midway in their progress. More than half disappear never to return. The remainder come back, one by one, to die in uraemia after a period during which they were perfectly well, as far as they knew, or as far as the clinician could tell by the use of the methods of inspection, palpation, percussion and auscultation.[2]

The diagram is intended to convey only an impression of the relative proportion of patients who can be said to be suffering in any way from the disease. It does not measure duration. That would be almost impossible in such a diagram because the duration is so variable. In general it is short in those patients whose lesions heal and long in those who die.

Figure 2 shows that in three-quarters of the cases healing occurs during the first year and that there is no instance of healing after the disease has lasted for five years. The average duration is about one year.

Among the patients who died as a result of the disease the average duration was 12 years. Figure 3 shows that in half the cases the

[2] Particularly in adults, the patients that a physician sees in the initial stage are apt to have the disease in an unusually intense form, while those in whom the symptoms are less pronounced quite frequently elude all observation. On this account no significance with respect to the disease as a whole can be attached to the fact that 26 out of this group of 51 patients ultimately died in uraemia.

duration exceeded 15 years and in one case, verified by the pathologist, the disease had lasted for 50 years. The reproduction in this figure of the duration of the healed cases gives a graphic demonstration of the contrast in the duration of the disease in these two groups. This

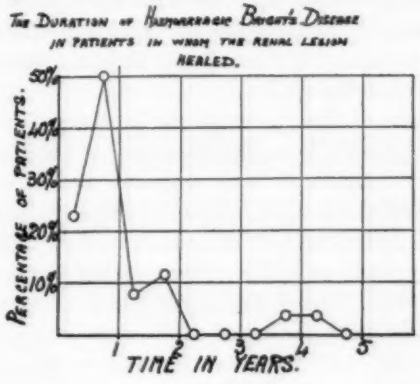

FIG. 2

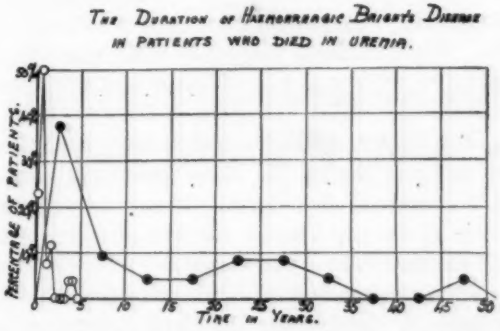

FIG. 3. ○ = patients in whom the lesion healed; ● = patients who died in uremia.

average duration of 12 years is surprising and since the chart comprises only 25 patients, this particular figure must be largely influenced by chance. But the average duration in all patients with Haemorrhagic Bright's disease now under observation in whom the onset was

observed, or is known, is already nearly five years, and there is every reason to expect that most of them will live for many years. This unfinished group contains 77 patients and the result confirms the conception that Haemorrhagic Bright's disease, when it does not heal, is a disease of long duration, often not a matter of years but of decades. This shows how large is the space in figure 1 in which there are no extra-renal symptoms. Haemorrhagic Bright's disease is thus a nearly symptomless disease.

The true course of these patients can be charted only by methods designed to measure the intensity and extent of the silent renal lesion. Without such measurements both physician and patient will remain in ignorance, and the patients will feel quite well until an insurance doctor or a Life Extension Institute examines their urine and suggests that they really ought to be ill. These methods have been described in detail elsewhere. One of them is intended to measure the nature and intensity, the other the extent of the renal lesion. In both cases their successful application depends as much on the patient as on the technique of measurement, for in order to remove those superficial and transient physiological fluctuations which conceal the underlying anatomical constancy, the patient must comply with conditions which are extreme. These methods purport to make quantitative and not merely qualitative measurements. That is how it has been possible in figure 4 to arrange patients, diagrammatically at least, in order of magnitude with respect to their renal lesion. And these methods attempt to measure during life those quantities with which the pathologist is concerned after death. That is why it may be hoped that they may fill the gap between the first certainty of the clinician and the final assurance of the pathologist.

In figure 4 the results obtained by these methods have been incorporated in figure 1. In this way the blank in-between space is now filled with a confused tangle of lines. Most of these lines are based on insufficient and defective evidence, but in each case there is at least a strand of objective fact and they represent quantitative judgments as to the relative status of each patient at every stage of his progress from the known beginning to the observed end in healing or in death.

But the group whose course is schematically represented in figure 4 is only a small part of all Haemorrhagic Bright's disease. It represents

only the clinician's disease. In order to obtain a more complete conception of the disease it is necessary to disentangle from the general mass of patients with Bright's disease those patients with Haemorrhagic Bright's disease who have not noticed or who have forgotten the beginning. The clinician knows, from his conferences with the pathologist, that some of all these patients with albuminuria and cylinduria have an undiagnosed Haemorrhagic Bright's disease. He knows, from such experiences as are depicted in figure 1, that no decisive

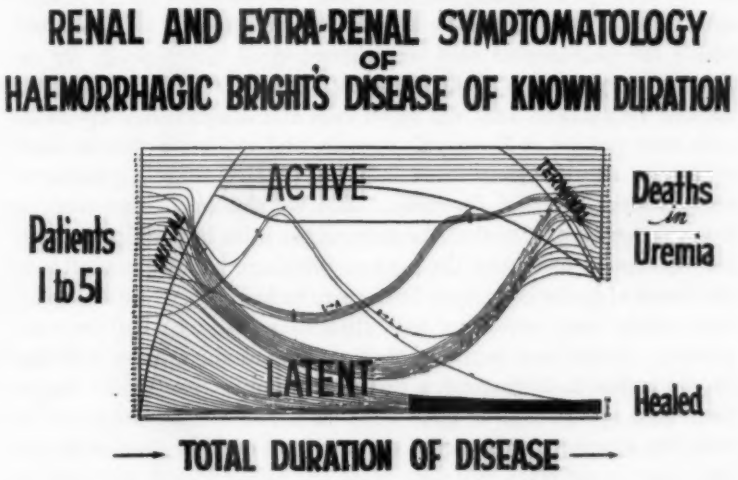

FIG. 4

enlightenment is to be expected from a study, no matter how detailed, of hypertension, arteriosclerosis, edema or cardiac failure, since in no one of these abnormalities is anything to be discovered that is distinctive of this disease. He knows, also, that even the sum of the results of all the ingenious methods for the measurement of the "partial" functions of the kidney is of no avail in this matter. So here, again, as in the case of the patients who were known to have Haemorrhagic Bright's disease, the clinician is obliged to make the most of the urine, the only material which is directly related to the object of his investigation. But now, lacking a knowledge of any

beginning, he studies the urine, not to measure the progress of the lesion, but first of all to find whether there exists in this or that individual case of albuminuria evidence of urinary abnormalities of the sort he has observed in known instances of Haemorrhagic Bright's disease.

For a time, towards the middle of the nineteenth century, the urine of patients with proteinuria and cylinduria was studied by clinicians with a good deal of hope. For it seemed reasonable to expect that a distinctive type of urinary sediment might be found in such a disease as this, which was known to begin with macroscopical bleeding, and which the pathologists said was characterised histologically by an inflammatory reaction in the glomerular tufts. In fact, their sections showed very clearly that red blood cells and desquamated epithelial cells were present in Bowman's capsule, and within the tubule these cells were seen conglomerated into casts which were in process of being floated out into the urine. But we also know that nothing came of these hopes, so that the study of the urine has gradually fallen into disrepute, until now the modern physician leaves the matter in the hands of junior internes or laboratory technicians. One reason for this neglect may have been that altogether too much had been expected. It had been supposed that a glance at the urinary sediment should suffice to distinguish a case of Haemorrhagic Bright's disease from such a degenerative renal lesion as is now termed nephrosis, or from the atrophic lesions which are the result of renal arteriosclerosis. But there is not often any such quick and ready answer and that for the very good reason that there is no such thing as a purely inflammatory, degenerative, or atrophic renal lesion, and so it is illusory to look for correspondingly distinctive urinary sediments. The problem requires a quantitative differentiation. This involves determinations of the rates of excretion of the formed elements in the urine. And when this is done it is found that, in theory at least, qualitative methods must be altogether abandoned, since everyone has protein, casts, and blood in his urine and there is no qualitative difference between a patient dying of Bright's disease and any healthy individual. This involves a quantitative definition of Bright's disease from the point of view of the urine. We may say that anyone has Bright's disease who excretes more than 100 mgs. of protein and

more than 5000 casts in a 12-hour urine. If, for the moment, such an arbitrary numerical definition is accepted and sediment counts are made on all patients who fall within it, the rates which are obtained tend to fall into three main groups. The median or average rates are shown in figure 5.

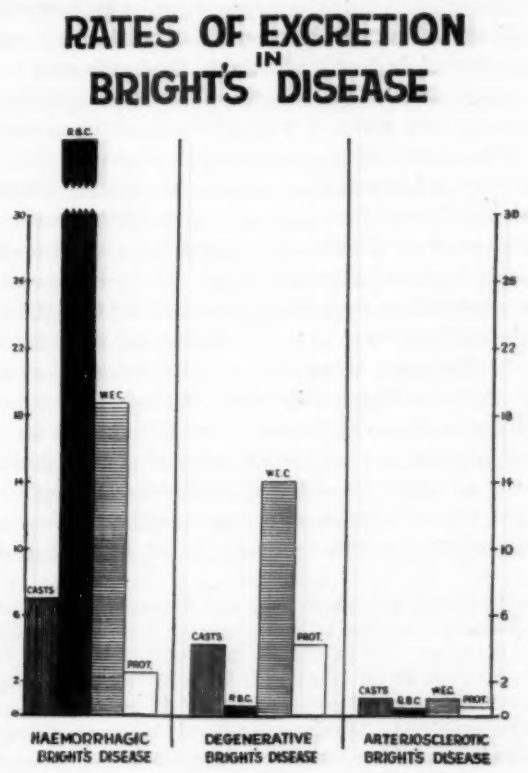

FIG. 5

One is characterised particularly by a great increase in the number of red blood cells, and was therefore called, in a purely descriptive manner, Haemorrhagic Bright's disease. In the second the rate of excretion of degenerated epithelial cells of casts and of protein is

markedly increased and so the group was called Degenerative Bright's disease.[3] In the third group there is no very pronounced increase in any of the measurements, and since the patients on whom these counts were made had almost always hypertension and arteriosclerosis, it was called Arteriosclerotic Bright's disease.

This classification of Bright's disease remains arbitrary and meaningless until it is shown to have both a clinical and a pathological significance, clinical, in that it is found to be of assistance in diagnosis and in the study of etiology and prognosis, pathological, in the sense that the groups into which it separates patients correspond to histological differences in the structure of their kidneys.

In regard to this latter matter, however, the variation in the pathological classifications of the renal lesion in Bright's disease should be enough to prevent the clinician from regarding the pathologist as the arbiter of any final and absolute truth. In some respects his difficulties are greater than those of the clinician, for though his material is susceptible of the most detailed elaboration in space, it has no extension in time, but is restricted to the moment of death. In pathology, the time element is added through the memory of analogous lesions seen in an earlier stage of evolution. So the judgments of pathology depend not only on an estimate of the relative amount and intensity of each type of lesion but involve conceptions of their development and their influence on one another. The purpose is to separate the significant from the insignificant, that which determines

[3] Degenerative Bright's disease includes such diverse renal lesions as are found in metallic poisoning, jaundice, malaria, pregnancy toxemia, amyloidosis, and all the bacterial infections. The justification for grouping them together rests on the observation that these are all lesions which in themselves are not progressive and which tend to revert to normal on the cessation of the pathological conditions with which they are associated. In this respect the whole group is distinguished from the irreversible lesions which occur in Haemorrhagic Bright's disease and in Arteriosclerotic Bright's disease. But though all the various lesions included in Degenerative Bright's disease are characterised by an abnormal rate of excretion of degenerated epithelial cells, an average of sediment counts from patients with such a multitude of different diseases, with such varying degrees of intensity of lesion, would have little meaning. So the averages which are charted in figure 5 are derived from counts made on 10 patients with Cryptogenic Degenerative Bright's disease—the so-called "genuine nephrosis."

from that which is determined. In such a variously difficult undertaking disagreement can be anticipated between pathologists, at least in matters of detail, and when at the end of the development of a renal lesion whose clinical course has been hidden from us we appeal to the pathologist for enlightenment, it will not be in any spirit of blind faith, but only with the recognition that under such circumstances his views are apt to be more positive and better founded than our own. They do in fact often have a decision and clarity which is quite comparable with the certainty of the clinician at the beginning of a Haemorrhagic Bright's disease.

Dr. Oliver has examined the kidneys of a consecutive series of patients with proteinuria and cylindruria who had been classified during life in accordance with measurements of the rates of excretion of protein and formed elements. One of the general results was his recognition of the fact that the material was not susceptible of classification on the basis of absolute pathological distinctions. It was *not* found that in some instances the lesions were inflammatory, in others degenerative and in still others atrophic; on the contrary, in every case all three types of lesion were demonstrable. It was *not* found that in some cases the glomeruli were affected, in others the tubules and in still others the vascular and interstitial tissues; on the contrary, in every case all these tissues were involved. In accordance with this view then even the clearest pathological differentiations in regard to the kidney in Bright's disease are of a quantitative not of a qualitative nature. In this respect the pathological findings are in accordance with the conclusion to which the clinician is forced whenever he leaves the beginning of Haemorrhagic Bright's disease.

For the purposes of correlation the pathological study may be divested of all its special pathological interest, and its results may be ordered under certain type lesions which have been defined and called "glomerulitis," "parenchymal degeneration," "interstitial proliferation," and "arteriosclerosis or endarteritis." Judgment as to their presence or absence in significant degree may be designated by the symbols + and − or by the sign ± where such lesions may or may not be present. In this manner table 1 has been constructed.

The table shows that glomerulitis is found in significant degree only in the group called Haemorrhagic Bright's disease. Since this con-

clusion is based on a series of 45 patients who died at all stages of the disease, except at the very beginning, we are justified in attaching an anatomical and pathological significance to the quantitative urinary abnormalities on account of which they were placed during life in this group. The high rate of red blood cell excretion, which is one of the significant features of the initial stage, carries on to the end and so we are enabled to recognise the condition in patients in whom its clinically characteristic beginning has been long forgotten.

Having by such methods bridged the gap between the relative certainties of the clinician at the beginning and the pathologist at the end, it was possible to include in the picture of the urine in this disease (fig. 5) measurements made on many patients in whom there was no knowledge of any beginning. But this sum of all observations, though

TABLE 1

CLINICAL GROUP	GLOMERULITIS	PARENCHYMAL DEGENERATION	INTERSTITIAL PROLIFERATION	ARTERIOSCLEROSIS OR ENDARTERITIS
Haemorrhagic	+	±	±	±
Degenerative	−	+	±	±
Arteriosclerotic	−	±	+	+

it suffices to show differences when contrasted with Degenerative or Arteriosclerotic Bright's disease, is not particularly helpful in determining the status of the individual patient, because, as the lesion leaves the beginning, it may follow different paths towards the two ends of healing or of death, and each of these paths is marked by quantitative differences in the urinary sediment. So, although these various stages of the disease merge insensibly into one another, each has its individual characteristics and for purposes of description each may be treated separately.

It is shown in figure 6 that at every stage the special peculiarity of the disease as a whole, *i.e.*, the high rate of red blood cell excretion, is maintained. But in each stage there are changes in the relative proportions between the rates of cast, red blood cell, white blood cell and epithelial cell and protein excretion.

In addition to these shifts in the relative rates of excretion there are

also changes in the sediment which are not susceptible of quantitative evaluation. It is not possible, for instance, to distinguish always between white blood cells and epithelial cells, yet it can be seen that in the Initial Stage there are many pus cells, while in the Terminal Stage these cells are quite clearly predominantly epithelial. These and other less definable differences combine to give a certain individuality of composition to the sediment of each stage. Figure 7 gives the average differential cast count for each stage.

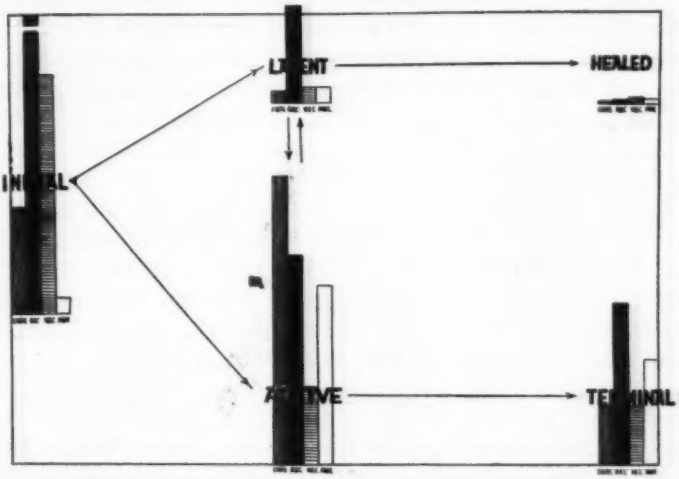

FIG. 6. The relative rates of excretion of (1) casts, (2) red blood cells, (3) white blood cells and epithelial cells, and (4) protein, in the different stages of Haemorrhagic Bright's disease.

It has been said, in relation to discriminations within what has been defined as Bright's disease, that it has been found necessary to base such differentiations on quantitative measurements. But in these differential cast counts there is one material element which has a qualitative significance. The blood casts which occur in the initial and throughout the earlier parts of the latent stage are truly pathognomonic of Haemorrhagic Bright's disease.[4]

[4] Other peculiarities worthy of mention are the threads of what are probably fibrin seen in some cases in the late initial stage; the large tubule cells full of

The typical Initial stage, as shown in figure 6, is not only the stage of the macroscopically bloody urine, it is the stage in which the greatest numbers of white blood cells and epithelial cells are found. If it were wise to tamper with long established terms, there would be something to be said in favor of speaking not of glomerular but of glomerulotubular nephritis, for this element in the sediment may be regarded

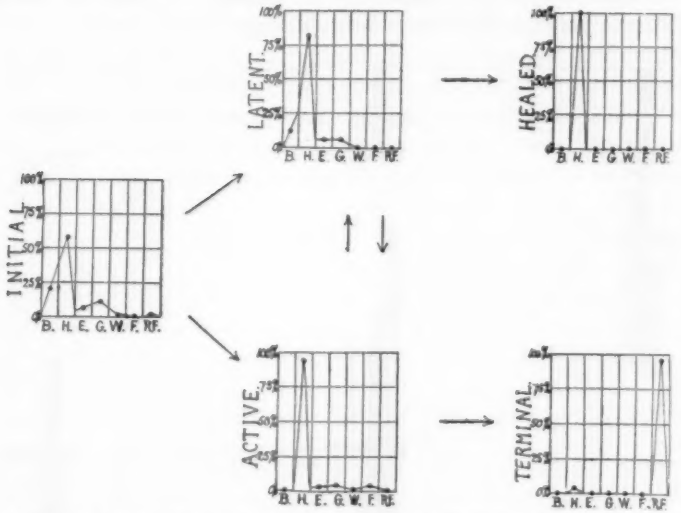

FIG. 7. AVERAGE DIFFERENTIAL CAST COUNTS IN THE VARIOUS STAGES

B = blood casts. E = epithelial casts. W = waxy casts. R. F. = renal failure casts. H = hyaline casts. G = granular casts. F = fatty cats.

as clinical evidence, which in lesser degree persists throughout all the stages, that the lesion is of such a nature as to lead to a marked increase in the death and desquamination of tubule cells.[5] In view of the

coarse granules or fat droplets often seen in the active stages of the disease; the very faint stromata which are all that is left of the red blood cells in the active and terminal stages, and the broad renal-failure casts of the terminal stage. Of these phenomena only the "fibrin" threads and the blood casts are peculiar to Haemorrhagic Bright's disease.

[5] There is sometimes more than this. In certain instances, not included in the median values plotted in figure 6, the numbers of white blood and epithelial cells

bleeding which we know comes at least predominantly from the glomeruli, and on account of our natural tendency to regard this sign as an indication of a disorganization of the glomerular endothelial and epithelial cells, whose function it is to prevent the passage of protein from the blood to the urine, the relatively low rate of protein excretion seen so often in the initial stage seems to be noteworthy and somewhat remarkable. In the Active stage when there is far less bleeding, the rate of protein excretion becomes much greater. It is in this stage that edema may reappear—but in a different form, for now it is soft and pitting instead of hard and brawny. Sometimes, but by no means always, there is a reappearance of hypertension but its form has also changed, for now it remains more or less constant and does not quickly fall to normal as in the initial stage. The sediment also is radically altered. Its most striking characteristic is the large number of narrow hyaline casts sprinkled over with finely shining fat droplets and epithelial cell inclusions either intact or reduced to granules. Between these casts lie many epithelial cells, some of them swollen with coarse granules or doubly refractile fat droplets, and the faint stromata of lysed red blood cells which show that here there is more than degeneration. The Latent stage is symptomless in those patients who are progressing towards complete healing, and for a very long time even in those who are going to die in uremia there may be no extra-renal symptoms. But as the years go by, the long maintained approximately normal amount of functioning renal tissue begins slowly to decrease and before the final failure there is a moderate increase in blood pressure levels and still later the development of clinically detectable arteriosclerosis. The Terminal Stage is the stage of true uremia. The character of the sediment is altered by the fact that the urine is now dilute and so there are no hyaline casts and the red blood cells are lysed. All the casts are now of epithelial derivation, and as the uraemia deepens, they become broader.

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rose in the initial stage into the hundreds of millions and exceeded the level of red blood cell excretion. This suggests that there was an associated pyelitis, though its occurrence has not yet been definitely connected with the history occasionally given by patients that during the first few days of the disease they suffered from pain in the lumbar region and pain and frequency in micturition.

These stages have, of course, no separate existence of their own. They are simply names for different paths of development of the renal lesion. And there is much that is arbitrary in the means adopted for their definition. For the median sediment results shown in figure 6 and in figure 7 were compiled from counts made at times when the

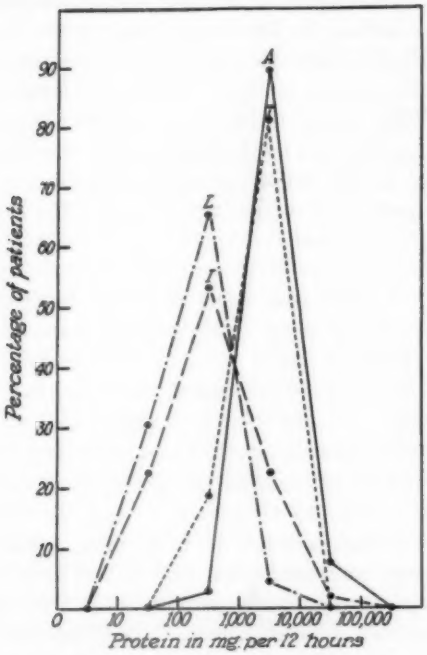

FIG. 8. FREQUENCY DISTRIBUTION IN RATES OF PROTEIN EXCRETION IN THE VARIOUS STAGES

I = initial stage. A = active stage. L = latent stage. T = terminal stage.

patients were thought to be approaching the center of the streams called "latent," "active" and "terminal." But there are no real divisions in the sense that it is possible to say exactly when a patient passes from the initial to the latent stage, from the latent to the active, from the active to the latent, or at what moment he can be said to be in the terminal stage. The disease itself is an uninterrupted

and continuous process. And it is much more rich in surprise and variation than is suggested by such a diagram as figure 4. If it had been possible to plot the true course of each individual in that group, the whole space would probably have been filled by an inextricable tangle of crossing lines.

The graphs give no indication of the great quantitative differences observed in different individuals. When frequency distributions are constructed, they are all so exaggeratedly skewed that it is necessary to use a logarithmic scale in order to portray them conveniently. An example is shown in figure 8 which gives the distribution of rates of protein excretion in the various stages.

Yet in spite of the absence of any sharp boundaries and in spite of these great individual variations in all the measurements, there

TABLE 2

The stage in which patients were found when they were first seen

Total number of patients = 464

	per cent
Initial stage	17
Latent stage	37
Active stage	21
Terminal stage	25

remains in their combination something sufficiently distinctive to allow one, with some assurance, to leave the clinically safe ground of the beginning and to recognise patients with this disease at any stage in which they present themselves. And so it is possible, though in some instances only doubtfully, to assign each patient to the stage in which he was found when he was first seen. The distribution is shown in table 2.

Though every effort was made to see patients as early as possible in the disease, it will be noted that the great majority were first seen in the latent, the active or the terminal stages. It seems, at first, strange that anyone could be afflicted by such a peculiar train of symptoms and not notice and remember an occurrence so remarkable. And yet the ordinary not too self-observant individual has his attention focussed on himself first of all by sensations of pain, discomfort,

weakness, not primarily by the objective signs which are to us significant. Unless there is added to the cardinal signs, those symptoms—headache, vomiting, convulsions—which we usually ascribe to cerebral edema, even the initial stage of Haemorrhagic Bright's disease is devoid of any noteworthy subjective symptoms.[6] In arranging in order of magnitude the sediment results in the initial stage it chanced that the one which it was thought indicated the most intense lesion was from a patient who came for no other reason than curiosity. It had been his habit to weigh himself every morning and he wanted to know how it had come about that his weight had suddenly increased by more than ten pounds. He did not know that his urine had a dark mahogany color, that he had a hypertension, and that he had a slight generalised edema. It must, then, be recognised that the whole story of Haemorrhagic Bright's disease is not completely given even in the combined experience of the clinician and the pathologist. It may be that the majority escape observation and pass in a happy ignorance from an unnoticed beginning through a symptomless latent stage to a perfect recovery.

These observations on the natural history of Haemorrhagic Bright's disease are incomplete and fragmentary and still so disconnected that it is not possible to use them for the construction of any convincingly concrete conception of the disease. But there does seem to emerge an outline which is simpler than any which can be derived from the acceptance of current views as to the existence of several pathogenetically distinct forms of glomerular nephritis. It is true that in the "embolic glomerular nephritis" a concurrent septicemia may greatly alter the clinical course and may sometimes produce a distinctive type of glomerulitis. But since in patients with streptococcal septicemias a connected series of examples may be observed which at one extremity merges insensibly with the central characteristics

[6] The proportion of patients seen in the initial stage is certainly much higher in children than in adults, because their mothers observe and are frightened by the peculiar appearance of the urine. This circumstance is probably a considerable factor in the formation of the generally accepted view that the prognosis is more favorable in children than in adults. That opinion may be correct, but it does not rest on a comparison of all cases of Haemorrhagic Bright's disease in children with all cases of Haemorrhagic Bright's disease in adults.

of the disease as a whole, it is not clear that this group of patients should be regarded as suffering from a quite separate form of nephritis. But apart from this generally recognised complication, it is not uncommonly supposed that there is a special sort of glomerular nephritis which from the beginning and throughout its whole course has been "chronic," using that term in the pathological sense as indicating a relatively "low-grade" and inactive lesion. This belief is based an negative evidence. It rests on the absence of any history or observation of the unquestionably "acute" initial stage and on the predominant inactivity of the lesion in the small fibrous kidneys which are found at post-mortem examination. But when it is observed how easily even a very active initial stage may pass unnoticed, and when it is found that patients seen originally in a typical acute onset die many years later of uraemia and have the same small fibrous kidneys, and when, in spite of waiting and watching, no example of the slow and insidious onset and course of this hypothetical disease is ever seen, it seems simpler to suppose that all cases, even those not observed until the kidneys are already sclerosed, may originally have been acute.[7] It is also quite generally supposed that there is a "focal glomerular nephritis" which should be distinguished from "diffuse glomerular nephritis" because it has a distinctly different pathogenesis, prognosis and pathology. Clinically, it is a presumably benign

[7] The clinical evidence derived from sediment counts is necessarily one-sided. The protein, the casts, the red blood cells and the white blood cells and epithelial cells are direct manifestations only of that part of the total lesion which is active. They come from still functioning renal elements, and their excretion stops whenever the disease leads to a complete cessation of function. They give no information at all about the slow atrophy and fibrosis, the interstitial proliferation and the endarteritis which are such important elements in the disintegration of the normal architecture of the kidney. The occurrence of such processes may be inferred by the clinician from a gradual decrease in the amount of actively functioning renal tissue, but that is only an inference based on general pathological experience and never immediate and direct. But the fact that the clinical evidence as to the nature of the lesion is one-sided does not detract from the positive assurance it provides that the activity of the lesion at the beginning carries on, though usually in diminishing degree, to the very end, and that histological examination gives warrant for the belief that an active component may have been at work throughout the whole course even of the most chronic cases.

disease, without hypertension or arteriosclerosis, whose only clinical manifestation is a slight continuous hematuria. But when these patients are watched for years and it is observed that in some the renal lesion heals and that in others, though often very slowly, there is in the end the gradual development of hypertension, arteriosclerosis and ultimately of uremia, and when the pathologist fails to find any essential difference between these kidneys and those of other patients with a similar clinical course in whom it has happened that the initial stage was observed, it becomes simpler to suppose that this "focal glomerular nephritis" is really only the latent stage of Haemorrhagic Bright's disease. It seems safer to hold fast only to what has been actually seen through to the end and, provisionally at least, to look on these supposedly distinct entities as only partial aspects of a disease whose entire course has not yet been fully revealed.

A STUDY OF THE LATE EFFECTS OF THE TOXEMIAS OF PREGNANCY (EXCLUDING VOMITING AND ECLAMPSIA)

C. H. PECKHAM AND M. L. STOUT

From the Department of Obstetrics, the Johns Hopkins Hospital and University

It is a matter of clinical experience that many obstetrical patients who have had a toxemia during pregnancy, which apparently has disappeared in the puerperium, return some months later with signs and symptoms of a definite chronic nephritis. In an effort to obtain more information concerning the toxemias of pregnancy a special "toxemia clinic" was inaugurated in 1927 in the Obstetrical Dispensary of the Johns Hopkins Hospital. It has been the province of this clinic not only to supervise pregnant women showing evidence of toxemia but also to follow their course after their discharge from the hospital. As a result of this prolonged observation, one of us (P), in 1929, reported that 23 per cent of 74 eclamptic women showed a definite chronic nephritis within a year following delivery.

In this paper we have attempted a similar study of the other toxemias of pregnancy (excluding vomiting) in an effort to ascertain how many of these patients will ultimately show a definite nephritis, as well as to attempt to ascertain from a study of their course during pregnancy whether any signs or symptoms were noted which should have enabled us to predict the ultimate outcome at an earlier date.

For this purpose we have attempted to trace all patients who suffered from pre-eclampsia, low reserve kidney, nephritis or unclassified toxemia (according to the hospital diagnosis) who have been delivered on the service during the four years ending May 31, 1930, and to secure their return to the clinic for reexamination and study. Many of these patients were already regular visitors to the toxemia clinic, and through the activities of two social workers it has been possible to secure the return of many others.

Table 1 shows the total cases of toxemia admitted to the hospital during this four-year period, together with the diagnosis made in each

instance on the discharge of the patient from the hospital. It may be stated that the classification was made according to the schedule proposed by Stander and Peckham in 1926. The total admissions on the Indoor service during this time were 6,411—giving a toxemia incidence of approximately 1 to every 10 patients. It will be noted

TABLE 1

Total cases of toxemias of pregnancy (June 1, 1926, to May 31, 1930)

HOSPITAL DIAGNOSIS	CASES	DIED	TRACED ALIVE
Vomiting (total admissions)	46	1	
Eclampsia (patients delivered)	61	8	
Pre-eclampsia (patients delivered)	46	2	32
Low reserve kidney (patients delivered)	323	0	190
Nephritis (patients delivered)	114	7	84
Unclassified (patients delivered)	62	3	37
Total	652	21*	343

* Seven of 21 deaths due to causes unrelated to toxemia.

Deaths include those of patients succumbing in hospital, together with those occurring elsewhere at a later date.

TABLE 2

Data on cases investigated for this study

	NUMBER	PER CENT
Total patients	515	
Total pregnancies	545	
Total deaths (known)	12	2.33
Total reëxamined	343	66.60
Total not found	160	31.07
Of total patients reëxamined:		
Definite nephritis	137	39.94
No nephritis	198	57.73
Diagnosis uncertain	8	2.33
Total	343	

that the cases diagnosed as "low reserve kidney" make up roughly half of the total number, while "pre-eclampsia" comprises only 7 per cent. That the former figure is too high and the latter too low will be shown later.

Table 2 shows the gross results of our attempt to follow up the

patients in the above groups. It will be seen that two-thirds of the total number returned to the dispensary and were examined for signs and symptoms of chronic renal involvement. A number of other patients were found to be alive but refused to return for examination and accordingly are not included in the group. A diagnosis of chronic nephritis was made whenever a definite hypertension existed, systolic pressure over 150 or diastolic above 100, whenever persistent and definite albuminuria existed; but such a diagnosis was not made when other causative factors for the above signs, such as goitre or cardiac disease were present. In many instances the eyegrounds were examined. The patients were also questioned concerning symptoms as headache, visual disturbances or nycturia, but in no case was a positive diagnosis made on the basis of symptoms alone, they merely being regarded as confirmatory evidence.

It may be stated that all of these patients were examined at least four months after delivery and in most cases one to four years after delivery. As will be seen from the table, 40 per cent of them were found to have definite nephritis; 58 per cent had no renal involvement, while in approximately 2 per cent the diagnosis was still uncertain. Obviously, a great many of these patients had nephritis prior to the pregnancy.

It should be noted that in approximately one-fourth of the cases diagnosed as pre-eclampsia or low reserve kidney, the original diagnosis was incorrect and should have been nephritis, while one-fifth of the patients who were thought to have nephritis were found later to have no permanent renal involvement.

A detailed study was made of the course of pregnancy and the puerperium in all of the cases traced. This study included the following information obtained from the hospital records; age, color, and parity; history of previous illness predisposing to nephritis; the high point of blood pressure (systolic and diastolic); largest amount of albumin in the urine and the presence or absence of casts; oedema; 'phthalein and renal concentration tests; length of labor; duration of pregnancy at the time of appearance of hypertension or albuminuria and the time elapsing between their appearance and delivery; the outcome to the child; and blood pressure and albumin on discharge. Finally, the blood pressure and albuminuria were noted in such patients as made the routine postpartum visit six weeks after labor.

Table 3 gives, in the first place, the age of the patients at the time of delivery and shows that the mean age of the nephritic women exceeded by almost six years the age of those who later were found to be normal. Approximately a quarter of the nephritic patients were under twenty-five years of age, while two-thirds of the non-nephritics fall into that age group. On the other hand, almost a third of the nephritic patients were over thirty-five, as contrasted with one-

TABLE 3*

Data on age, color and parity of patients returning with or without nephritis

	NEPHRITIC		NON-NEPHRITIC	
	Number of patients	Per cent	Number of patients	Per cent
Age:				
Under 19 years	11	8.03	66	33.33
20 to 24 years	23	16.79	66	33.33
25 to 29 years	30	21.90	29	14.65
30 to 34 years	28	20.44	21	10.61
35 to 39 years	30	21.90	11	5.56
40 years and over	15	10.95	5	2.53
Total	137	100.01	198	100.01
Mean age	29.72220 years		23.96465 years	
Color:				
White	53	38.69	90	45.45
Black	84	61.31	108	54.55
Parity:				
Para 0	26	18.98	132	66.67
Para X	111	81.02	66	33.33

* In this and subsequent tables we include only 335 patients, having omitted the 8 in which a definite diagnosis could not be made at the time of reëxamination.

twelfth of those returning to normal. Very little difference was noted between the two races. The fact that there were more black women than white in the group is probably due to the greater ease with which the former were persuaded to return for examination. As might be expected, the existence of nephritis was noted chiefly among multiparae. Moreover, it seems significant that two-thirds of the non-nephritic toxemias occurred in primigravidae, while more than four-fifths of the nephritic women had had previous pregnancies.

Very little comment on table 4 is necessary. It is noteworthy that one can more frequently obtain a past history of relevant disease in

TABLE 4

RELEVANT PREVIOUS HISTORY	NEPHRITIC	NON-NEPHRITIC
Toxemia, previous pregnancy	22	12
Eclampsia, previous pregnancy	9	3
Nephritis, previous pregnancy	19	0
Typhoid fever	2	5
Scarlet fever	2	6
Rheumatic fever	1	2
Diphtheria	0	2
Pyelitis	0	2
Tuberculous kidney	0	1
Cardiac disease	1	0
Total	56	33

TABLE 5

Systolic blood pressure in hospital

	NEPHRITIC		NON-NEPHRITIC	
–129	1		2	
130–139	0	5.83%	6	19.19%
140–149	7		30	
150–159	19		38	
160–169	24		39	
170–179	22	70.81%	37	74.74%
180–189	19		18	
190–199	13		16	
200–209	12		9	
210–219	5		2	
220–229	2		1	
230–239	5	23.35%	0	6.06%
240–249	1		0	
250–	7		0	
Mean	183.46710		167.47474	

the nephritic (40.83 per cent of cases) than in the non-nephritic (16.67 per cent) group. Twelve patients, 9 of them nephritics, had suffered

from a previous attack of eclampsia, and in 34 cases the toxemia was recurrent. It seems significant that nephritis later developed in 22

TABLE 6

Diastolic blood pressure in hospital

	NEPHRITIC		NON-NEPHRITIC	
– 89	2		1	
90– 99	8	51.82%	30	68.18%
100–109	22		52	
110–119	39		52	
120–129	21		34	
130–139	24	41.60%	17	30.30%
140–149	12		9	
150–159	2		2	
160–169	1	6.57%	1	1.51%
170–	6		0	
Mean.....	123.02920		114.64647	

TABLE 7

AMOUNT	NEPHRITIC		NON-NEPHRITIC	
Albumin content of urine (in hospital)				
grams				
0	16	11.67%	18	9.09%
Trace	41	29.93%	64	32.32%
–0.9	21		29	
2–1.9	29	51.83%	35	51.51%
2–2.9	15		24	
3–4.9	6		14	
5–9.9	8	6.56%	10	7.07%
10–	1		4	
Casts found in urine (in hospital)				
Present	52	37.95%	47	23.73%
Absent	85	62.04%	151	76.26%

women whose previous toxemia had seemed mild and had apparently vanished entirely during the puerperium.

Table 5 shows that the mean systolic blood pressure was significantly higher in the nephritic patients, and indicates that when the systolic blood pressure does not reach 150 mm. the patient probably has not and will not develop nephritis. On the other hand, we should consider as a potential nephritic any woman whose pressure reaches

TABLE 8

Renal function tests in hospital

PHENOLSULPHONPHTHALEIN TEST PER CENT EXCRETED	NEPHRITIC		NON-NEPHRITIC	
–9	0		0	
10–19	1		0	
20–29	3	20.34%	3	13.56%
30–39	2		0	
40–49	6		5	
50–59	11	42.37%	17	45.76%
60–69	14		10	
70–79	11	37.29%	16	40.68%
80–	11		8	
Not made	78		139	
Mean	62.79661		63.81355	
MOSENTHAL TEST POINTS CONCENTRATED				
0–4	5	30.56%	8	34.94%
5–9	17		21	
10–14	26	69.44%	27	65.06%
15–	24		27	
Not made	65		115	
Mean	12.29165		11.89760	

200 mm., unless she has eclampsia or a symptomatic pre-eclampsia, as all twelve of the non-nephritic women with such a degree of hypertension had suffered from pre-eclampsia.

It is thus seen that the mean diastolic blood pressure is also higher in the nephritic group. As with systolic pressure, extreme elevations

(above 150 mm.) except in cases of pre-eclampsia seem to indicate that permanent renal damage will occur.

Table 7 shows that the amount of albumin in the urine gives very little information as to the end result of the toxemic process, as marked albuminuria (over 5 grams per liter) is apparently seen as often in nephritis as in the low reserve kidney—pre-eclampsia group. On the other hand, most of the 9 women ultimately found to be nephritic and whose urine had this content of albumin were observed early in pregnancy and were apparently normal until the last trimester. They also had marked hypertension and were regarded clinically as typical cases of pre-eclampsia. Since it is known that eclampsia may leave a patient with permanently damaged kidneys it seems likely that a toxemia as severe as pre-eclampsia might well end similarly.

TABLE 9

Oedema (in hospital)

AMOUNT	NEPHRITIC		NON-NEPHRITIC	
0	43	31.38%	83	41.92%
Slight	54	39.42%	70	35.35%
Moderate	25	18.24%	21	10.60%
Marked	15	10.95%	24	12.12%

The presence or absence of casts gives very little information, except that they are found somewhat more frequently in women later returning with nephritis.

It has been felt for some time that no important information is to be gained during pregnancy from the phenolsulphonphthalein test for kidney function. That this is true is shown in table 8. There is a slightly greater incidence of nephritis when the reading is low (under 50 per cent). However, the mean percentage of excretion in the nephritic and non-nephritic groups is practically identical.

An examination of the results of the Mosenthal renal concentration test reveals that it, too, is of little value as a help to diagnosis. Indeed, the mean range of variation in points of specific gravity would indicate a slightly better ability to concentrate the urine on the part of the nephritic patients.

The amount of oedema is charted according to clinical impression

at the time of admission to the hospital. Our observations indicate that its presence or absence, as well as its degree, if any is present, affords no criterion as to the type of toxemia at hand.

Table 10 is given merely to illustrate that although there is no essential difference between the duration of labor in the two classes of cases, yet the toxemic woman in general seems to have a shorter labor than the normal patient, despite the frequency of inductions and premature labors.

The foetal mortality, as was to be expected, was higher in nephritic than non-nephritic women, being 17.93 and 10.00 per cent, respec-

TABLE 10

Duration of labor (spontaneous, operative or induced, total pregnancies)

HOURS	NEPHRITIC	NON-NEPHRITIC
– 5.9	45	53
6–11.9	37	68
12–17.9	19	36
18–23.9	7	13
24–29.9	5	14
30–	15	13
?	2	0
Mean.....	11.95314	12.13704
Caesarean sections	11	6
Abortions	15 (12 Ther.)	2 (1 Ther.)
	156	205

tively, in the two groups. It may be stated that the gross foetal mortality rate (still-born and neonatal) for the entire Clinic is 9.51 per cent, so that for the non-nephritic toxemias the foetal mortality is not significantly increased. The high incidence of prematures (under 2500 grams) is partially responsible for the increased rate in nephritis and, if these are excluded, the mortality rate falls to 13.16 per cent in nephritic as compared with 5.92 per cent in non-nephritic women. There was an increased incidence of twins, 1 in each 31 deliveries, as compared with the normal figure, which is usually given as 1 in 89.

An attempt was made next to study the relations between the two types of toxemias and the time when hypertension and albuminuria were first observed during the pregnancy. It was found that in the non-nephritic group the patient had usually already been under observation for some time before signs appeared. On the other hand, over two-thirds of the women later showing nephritis were already abnormal when first seen. We have, therefore, subdivided the nephritic group according to whether the patients had hypertension or albuminuria when they first came under observation, or developed them at a later date. A study of the above table reveals that in only 7.34 per cent of the non-nephritic cases did these signs become manifest before the seventh month. In the majority of the nephritic cases

TABLE 11

RESULTS TO CHILD	NEPHRITIC	NON-NEPHRITIC
Patients	137	198
Pregnancies	156	205
Abortions	15	2
Infants	145 (twins 4)	210 (twins 7)
Alive	119	189
Dead—after viability	26 (17.93%)	21 (10.00%)

we do not know when the break occurred, yet we can state with certainty that in over half of them abnormal signs were present prior to the last trimester of pregnancy. On the other hand, 18.71 per cent of the women that later developed nephritis were observed in the dispensary from early pregnancy and developed signs of toxemia only after the seventh month. We cannot say with certainty that such women owe their nephritis to the toxemia of pregnancy, but the paucity of signs or symptoms in the past history, together with the fact that they were clearly normal in the earlier months of pregnancy, makes this contention extremely probable. It will be observed that the average time of "break" is two months earlier in the nephritic than in the non-nephritic patients.

A study of the time elapsing in months between the appearance of hypertension or albuminuria to delivery in these patients shows that pregnancy continued for more than three months in less than 4 per

TABLE 12

Time of appearance of hypertension or albuminuria in months of pregnancy

MONTHS	NEPHRITICS			NON-NEPHRITIC
	Signs present at first visit	Signs developed during observation	Total nephritics	Time when signs were first observed
0	0	1	1	0
-0.9	0	2	2	0
1-1.9	0	1	1	0
2-2.9	7	0	7	0
3-3.9	13	0	13 (52.26%)	0 (7.34%)
4-4.9	14	3	17	0
5-5.9	13	2	15	2
6-6.9	16	9	25	11
7-7.9	15	11	26	25
8-8.9	20	11 (18.71%)	31 (47.74%)	65 (92.66%)
Term	10	7	17	74
Mean.....	6.2714 months	6.7553 months		8.6186 months

Lapse of time from appearance of signs to delivery

MONTHS	NEPHRITICS		NON-NEPHRITICS
	Signs present at first visit	Signs developed during observation	
0	10	17	80
-0.9	20	4	25
1-1.9	21	11	50
2-2.9	16	5	15
3-3.9	10	3	6
4-4.9	10	0	1
5-5.9	12	3	0
6-6.9	6	0	0
7-7.9	3	0	0
8-8.9	0	1*	0
9-	0	3	0
Total.....	108	47	177
Mean.....	2.6297 months	2.8830 months	0.4831 months

32.90 per cent of nephritic patients carried more than 3 months.

3.95 per cent of non-nephritic patients carried more than 3 months.

* Nephritis developed between pregnancies

cent of the non-nephritic women, as compared with almost a third of those who later developed nephritic signs; an observation which apparently indicates that the longer the pregnancy continues after the appearance of toxemic symptoms, the greater are the chances of an eventual chronic nephritis.

TABLE 13

Blood pressure on discharge (systolic)

MM. HG	NEPHRITIC		NON-NEPHRITIC	
–109	9		36	
110–119	12	35.77%	52	77.44%
120–129	28		63	
130–139	39		27	
140–149	15	39.42%	13	20.51%
150–159	19		3	
160–	15	24.82%	1	2.05%
?	0		3	
Mean.....	136.38696		122.02564	

TABLE 14

Blood pressure on discharge (diastolic)

MM. HG	NEPHRITIC		NON-NEPHRITIC	
–79	21		74	
80–89	39	43.80%	83	80.51%
90–99	41		32	
100–109	18	43.07%	5	18.97%
110–119	10		0	
120–	8	13.14%	1	0.52%
?	0		3	
Mean.....	94.34307		83.56411	

Our observations on the blood pressure and albumin content of the urine at the time of discharge of the patient from the hospital illustrate the danger in many cases of attempting to make a final diagnosis of the type of toxemia at that date. It may be stated that the usual

toxemic patient leaves the hospital on the fourteenth day of the puerperium, while in severe cases they are kept for a much longer period.

Table 13 shows the systolic blood pressure at the time of discharge. As would be expected, the mean was higher in nephritic than in non-nephritic women, being 136 and 122, respectively. However, 35.77

TABLE 15

Albumin in urine on discharge

AMOUNT	NEPHRITIC		NON-NEPHRITIC	
grams				
None	92	67.15%	140	71.43%
Trace	33	24.08%	44	22.44%
–0.9	6	8.76%	9	6.12%
1–1.9	4		3	
2–	2		0	
?	0		2	

TABLE 16

Blood pressure six weeks after delivery (systolic)

MM. HG.	NEPHRITIC		NON-NEPHRITIC	
–99	0	4.05%	0	34.83%
100–109	0		3	
110–119	0		5	
120–129	3		23	
130–139	5	29.73%	27	48.31%
140–149	17		16	
150–159	10	66.22%	6	16.85%
160–	39		9	
?	63		109	
Mean.....	154.59460		136.46067	

per cent of the nephritic women left the hospital with a systolic pressure below 130, which serves to exemplify the effect of rest in bed in many cases of mild chronic nephritis. On the other hand, 22.56 per cent of the women who later returned as normal still had sufficient toxemic residua to give a pressure of 130 mm. or more, at least as late as fourteen days after delivery.

Table 14 shows that the diastolic pressure in general is definitely higher in nephritic than in non-nephritic women; but at the same time the reading on discharge frequently gives rise to erroneous conclusions. Although the mean reading in the former is definitely higher, yet in 43.80 per cent of the women the reading on discharge fell within normal limits. On the other hand, in 19.49 per cent of the women who later became normal, it reached 90 mm. or more.

From table 15 it is apparent that albuminuria on discharge, its presence, absence, or amount does not justify a prognosis as to the ultimate outcome of the toxemic process; for apparently as many

TABLE 17

Blood pressure six weeks after delivery (diastolic)

MM. HG.	NEPHRITIC		NON-NEPHRITIC	
–69	0		5	
70–79	3	10.81%	15	66.29%
80–89	5		39	
90–99	16		21	
100–109	18	45.95%	4	28.09%
110–119	13		5	
120–	19	43.24%	0	5.62%
?	63		109	
Mean.....	107.16216		87.13484	

women were discharged with albumin persisting in the urine in the non-nephritic as in the nephritic group.

Approximately half the women under discussion returned to the dispensary for examination six weeks after delivery, when the blood pressure was taken and the urine tested for albumin. Until recently, it was the general belief that if the process were not nephritic in origin, the blood pressure and urine would be found to be normal at this time. Table 16, however, shows that this is not absolutely true, as 4 per cent of the nephritic women had a systolic pressure below 130 mm. On the other hand, in almost two-thirds of the non-nephritic women the pressure was above this figure, while in one-sixth the reading was 150 mm. or over. This was a very surprising finding and

its explanation is not clear. It seems improbable that in such a large percentage of patients later found to be quite normal the previous toxemia could be held accountable. We know of no figures concerning the blood pressure of normal women late in the puerperium, and are at present obtaining a reading on every normal patient returning at that date.

That women later showing nephritis may have a normal diastolic pressure six weeks after delivery is illustrated in table 17. However,

TABLE 18

Albuminuria six weeks after delivery

AMOUNT	NEPHRITIC		NON-NEPHRITIC	
0	53	69.73%	77	85.56%
Trace	6	7.89%	7	7.78%
Definitely positive	17	22.37%	6	6.66%
?	61		108	

TABLE 19

*Ultimate diagnosis, toxemias of pregnancy**

TYPE	NUMBER OF CASES	PER CENT
Vomiting	30*	7.35
Eclampsia	35*	8.58
Pre-eclampsia	50	12.25
Low reserve kidney	148	36.27
Nephritis	137	33.58
Unclassified	8	1.96
	408	99.99

* Estimated on basis of percentage of other cases traced.

one-third of the non-nephritic patients showed a reading above 90 mm. As with the frequency of a high systolic pressure in this type of case the explanation is not evident. Possibly the effort on the part of a woman, whose strength has not yet returned to normal, to get herself and her infant ready and to make the trip to the dispensary may be sufficient to produce a transient hypertension. At any rate, we can state that even as late as six weeks after delivery we are frequently unable to predict the ultimate outcome to the patient; and for this

reason a final diagnosis cannot always be made with certainty until much later.

Table 18 illustrates that albuminuria may persist at least six weeks after delivery following non-nephritic toxemias. However, in only 6.66 per cent of such cases is more than a trace observed. It will be noted from table 16 that although more than a trace of albumin was observed in only 8.76 per cent of the nephritic women at the time of discharge from the hospital, yet at six weeks after delivery 22.37 per cent of them gave a positive test.

Finally, in table 19 we present the percentage incidence of the various toxemias of pregnancy as calculated from the final diagnoses which were made four months to four years after delivery. The cases of vomiting and eclampsia were not studied, and are included merely to give an idea of the relative incidence of the various types of toxemia. The table requires no comment and we wish merely to point out that one-third of the total number of patients with toxemia observed during this four year period either had nephritis preceding the onset of pregnancy or developed it following the toxemic attack.

DISCUSSION

The differentiation between a nephritic and a non-nephritic toxemia of pregnancy frequently offers great difficulties, so that prognosis as to the ultimate outcome to the mother is often impossible prior to delivery. A large percentage of women apparently suffering from a mild toxemia will be found to have definite chronic nephritis four or more months after delivery. On the other hand, many women who on discharge or even six weeks after delivery present persistent hypertension and albuminuria later return to normal and subsequently have uneventful pregnancies. This paper was undertaken in order to ascertain whether it would not be possible by a careful study of the clinical course of a large group of toxemic patients to find something which would render it possible to make an earlier and more correct diagnosis. Accordingly, an attempt was made to trace all toxemia patients, excluding those suffering from vomiting and eclampsia, who had been admitted to the Indoor service of the Department of Obstetrics of the Johns Hopkins Hospital during a period of four years. The return of 343, or two-thirds, of the total patients was accomplished,

and they were examined for evidence of permanent renal involvement, with the result that approximately 40 per cent showed definite signs of chronic nephritis.

It was found that the mean age was approximately six years higher in the nephritic than in the non-nephritic patients, and that a third of the former were over 35 years of age, while two-thirds of the latter were under 25. Four-fifths of the cases showing permanent renal damage occurred in multiparae, while two-thirds of the non-nephritic toxemias were seen in primigravidae. A previous history of toxemia or of illness relevant to nephritis was more frequently obtained in patients whose toxemia was ultimately found to be nephritic, but it was obtained only in less than half of them.

Analysis of the high point of blood pressure during the pregnancy showed that the mean systolic and diastolic readings were definitely higher in the nephritic women. In only 6 per cent of the non-nephritic cases did the systolic pressure reach 200 mm., while that figure was attained in 23 per cent of the nephritics. On the other hand, when the pressure at no time reached 150 mm., very few cases of nephritis developed. Furthermore, a very high diastolic pressure, above 150 mm., also usually indicates nephritis. In our experience, except in nephritic toxemia, such marked hypertension is only occasionally observed in frank and fulminating cases of pre-eclampsia. It is interesting to note that most of our cases of nephritis following a toxemia associated with marked hypertension had presented in the hospital what appeared to be a typical picture of pre-eclampsia; and since it is known that nephritis can develop after eclampsia it seems plausible that it may also follow severe and prolonged pre-eclamptic toxemia.

Our observations indicate that albuminuria and its extent do not afford a differential basis for diagnosis; and likewise the presence of absence of casts in the urine is of no diagnostic value. Also, the phenolsulphonphthalein and Mosenthal renal function tests are inconclusive and so are of little value during pregnancy in the differential diagnosis of the several types of toxemia; while oedema is noted equally frequently in nephritic and non-nephritic toxemias.

Very rarely (in only 7 per cent of cases) does a non-nephritic toxemia manifest itself prior to the seventh month of pregnancy and one is

fairly safe in predicting that a patient presenting hypertension and albuminuria before this time will, particularly if allowed to proceed to term, later show signs of a chronic renal disease. More than half of the nephritic patients were known to be abnormal prior to the seventh month. However, almost a fifth of the women later diagnosed as nephritic came under observation early in pregnancy and were apparently normal at that time, developing signs of toxemia only after the seventh month. It seems plausible that in many such cases the nephritis was directly due to the toxemia of pregnancy. We can not state that a toxemic patient is more likely to develop nephritis later if the process is allowed to persist for a number of months before delivery; there is, however, a certain amount of evidence in favor of such a belief, as only 4 per cent of the non-nephritic women were allowed to go over three months from the time of onset of hypertension or albuminuria, whereas a third of the cases later diagnosed as nephritis were observed for at least that length of time.

Naturally, the mean blood pressure on discharge from the hospital is higher in the nephritic group. Nevertheless, more than a third of the patients later found to be nephritic were sent home with a systolic pressure under 130 mm., and 44 per cent with a diastolic pressure under 90. This illustrates the fallacy in ruling out nephritis on the basis of a normal blood pressure after the patient has been in bed for some time. On the other hand, approximately one-fifth of the women later proven normal went home with a pressure above these limits. The presence or absence of albumin in the urine at this time occurred about equally in the two groups.

Six weeks after delivery the majority of nephritic women have a hypertension, although 11 per cent of them still show a diastolic pressure below 90 mm. However, almost two-thirds of the toxemic patients later returning to normal have a systolic reading above 130 and one-third of them a diastolic above 90 mm. Also, a seventh of this group still have albumin in the urine. The explanation for such persistence of hypertension and albuminuria is not clear, but it demonstrates that even so late in the puerperium one often cannot classify the toxemia as nephritic or non-nephritic with any degree of certainty.

The foetal mortality is high in both groups, due in the non-nephritic group chiefly to the presence of a considerable percentage of premature

infants. It is, however, much higher in the nephritic group, reaching 17.93 per cent, and excluding babies weighing less than 2500 grams, is 13.16 per cent.

Finally, the percentage incidence of the various types of toxemia is shown as based upon the corrected diagnosis made at least four months after delivery. Including all types the incidence of chronic nephritis is 34.42 per cent.

We believe that it is possible to diagnose properly most cases of toxemia at the time of discharge from the hospital. Indeed, within a moderate limit, such a diagnosis may be made before delivery. However, we have carefully reviewed each case in the series and have reclassified the hospital diagnosis strictly according to the criteria laid down by Stander and Peckham in 1926. This reveals that there was an error of 11 per cent in which certain cases of nephritic toxemia were diagnosed non-nephritic, or vice versa. Accordingly, we feel that, except in obvious cases, it would be well to defer classifying the toxemias, and thereby expressing a prognosis for a subsequent pregnancy, until at least four months after delivery. By so doing, the number of pregnancies complicated by nephritis will be greatly reduced. If, however, it is desired to make a diagnosis before delivery, it would seem that the period of pregnancy when abnormal signs first appear gives the best criterion, although age and parity together with the degree of hypertension may be of aid.

Finally, we wish to state that the renal function tests utilized by us up to the present time are of very little value during pregnancy. Indeed, the only satisfactory test seems to be the behavior of the patient in a subsequent pregnancy and we have followed 55 patients of the non-nephritic group through one or more subsequent pregnancies and labors and have found that the course was either normal or mildly toxemic.

CONCLUSIONS

1. Of a series of 545 consecutive deliveries of toxemic patients, excluding eclampsia and vomiting, 66.6 per cent have been reexamined four months to four years after delivery, and at that time 40 per cent of them have been found to have a definite chronic nephritis.

2. The differential diagnosis between nephritic and non-nephritic toxemia frequently cannot be made during pregnancy or the puerperium, and even at six weeks after delivery the diagnosis is sometimes incorrect.

3. Nephritis is seen more frequently in the older age groups and among multiparae. Two-thirds of the non-nephritic toxemias occur in women under twenty-five, and a similar proportion are primiparae.

4. A marked hypertension (systolic 200 mm. or more and diastolic 150 mm. or over) is more frequently associated with nephritis, although an occasional case of pre-eclampsia is seen with this reading.

5. Albuminuria and its amount is of no prognostic import. The presence or absence of casts in the urine likewise gives no differential information.

6. The 'phthalein and Mosenthal renal function tests give almost identical results in the two types of cases.

7. Oedema occurs in the same proportion of cases in the two groups.

8. Toxemic patients in general seem to have shorter and easier labors than normal; however, the foetal mortality is high, particularly in nephritis.

9. The blood pressure is higher on discharge in the nephritic type. However, many women who have nephritis leave the hospital with a normal blood pressure, while about a fifth of the women later returning normal still have hypertension.

10. Albuminuria on discharge is noted in relatively the same proportion of cases, nephritic or non-nephritic.

11. Even six weeks after delivery many normal women still have hypertension and albuminuria while a small number of nephritic patients appear normal in these respects.

12. Only 7 per cent of non-nephritic patients show hypertension or albuminuria prior to the seventh month of pregnancy, while over half the nephritics were known to be abnormal at that time. However, almost a fifth of the women who ultimately were diagnosed as nephritic were known to be normal until after the seventh month. This would seem to indicate that chronic renal damage may be a result of the toxemic process.

13. Excluding vomiting and eclampsia, one of every three women

seen with a toxemia of pregnancy will ultimately be found to have nephritis.

14. Except in perfectly obvious cases it seems better to defer the final diagnosis until four months after delivery, although a diagnosis intelligently made at the time of discharge from the hospital is incorrect in only one case in nine.

TREATMENT OF ANAEMIA OF INFANCY WITH IRON AND COPPER[1]

HUGH JOSEPHS

From the Department of Pediatrics, The Harriet Lane Home

There has been much dispute in the course of the past twenty or thirty or more years on the value of medicinal iron in the treatment of the secondary anaemias of infancy. The opinion has gradually been gaining that iron in large doses is curative, but opponents can still point to the failures of iron therapy. It is not my purpose to review the literature, since the main arguments are too well known to make such a procedure necessary. In 1900 Bunge was still a name to be reckoned with, and he had previously laid down the law that medicinal iron in therapeutic doses was not absorbed,—that iron, to be absorbed, must be given in the form of food. When, however, it was finally shown, about 1900, to Bunge's satisfaction by Abderhalden, in Bunge's own laboratory, that iron was absorbed, it was then said that medicinal or inorganic iron took no part in haemoglobin building, but that its effect on the blood-forming tissue was that of a stimulator. Here the matter was dropped by the physiologists, and the best way to give iron was left to the clinicians as a matter of practical therapeutics.

In the minds of the clinicians there had scarcely ever been any question but that iron was absorbed,—their experience in the treatment of chlorosis left little doubt on this point—but Bunge's insistence on the necessity for food-iron left its mark. On very little evidence the law was laid down that it was better to buy iron in the market than in the apothecary's shop. Eggs and leafy vegetables became the accepted sources of iron and attempts were made to find out what it was in these materials that aided the formation of haemoglobin. It has gradually come to be felt that medicinal iron is utilized in haemoglobin formation, and should be given, but that the effect is

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much enhanced by the inclusion in the diet of eggs and vegetables. Like many a "law" that is handed down from textbook to textbook, the evidence on which it is based has been lost in the obscurity of unread or misinterpreted articles, and we have now little more than a tradition. Starting with the tradition, Hart and Steenbock with their associates showed that all that was necessary for the cure of nutritional anaemia in a rat was a little copper in addition to iron.

The work reported in this paper is an investigation of the treatment of so-called "secondary anaemia" of infancy with iron and copper; and no attempt is made to discuss etiology or pathogenesis. The study was conducted on a group of infants between the ages of three months and two years. Premature babies in the first six months of life have not been included; they will form a group to be reported upon in a future communication. The treatment of anaemia during the course of an infection will not be considered; it need only be stated here that iron with or without copper supplement has little or no effect in such cases. I have brought together all my material, including some cases previously reported.

The cases could be divided into two groups: (1) Those in which there was an infection present when the anaemia was discovered; and (2) those in which there was no infection. In the case with infection it was found advisable to include a period of preliminary observation commencing at the time that the temperature became permanently normal, during which no iron was given but the child was placed on the feeding to be continued throughout the study. In the cases without infection, a preliminary period was frequently omitted in order to shorten the period of observation, or because it was considered unwise to delay treatment. In the second period of observation, ferric ammonium citrate, 10 per cent solution, was given, 2 cc. per kilogram of body-weight per day. In the third period, copper sulphate ($CuSO_4.5H_2O$) 0.5 per cent solution was given in addition to the iron, 1 cc. per kilogram of body-weight per day. The copper was always given in the milk, usually divided into two doses. In the infants to whom it has been given, I have never seen any disagreeable results, although in older children this dose may cause vomiting and diarrhoea. In a number of children the second period was omitted, so that the child was started immediately on iron and copper together.

TABLE 1

General summary of cases forming the basis for the investigation

NAME	NUMBER	AGE	DIAGNOSIS	PERIOD OF PRELIMINARY OBSERVATION					PERIOD OF TREATMENT WITH IRON ALONE					PERIOD OF TREATMENT WITH IRON AND COPPER					LATENT PERIOD	MAXIMUM RETICULOCYTES	
				Initial hgb.	Duration	Rise in hgb. 1st 4 days	Rise in hgb. total	Diet	Initial hgb.	Duration	Rise in hgb. 1st 4 days	Rise in hgb. total	Diet	Initial hgb.	Duration	Rise in hgb. 1st 4 days	Rise in hgb. total	Diet			
		mos.																		*per cent*	
Sc.	1	9½	Pneumonia	52	19	4	0	Milk, vegetables, egg												4.5	
Hol.	2	14	Pneumonia	37	18	8	10	General	47	8	5	5	General	52	5	14	17	General	3	10	
W. Th.	3	18	Pneumonia	47	7	0	0	Milk and farina	47	31	5	25	Milk and farina						7	8	
J. S.	4	18	Pneumonia	48	10	0	0	General	48	7	5	5	General	53	7	7	12	General	2	6	
Als.	5	24	Pneumonia	51	5	5	8	General												3	
P. C.	6	12	Pneumonia						37	28	6	17	General	54	7	6	6	General	10	5	
Ma.	7	19	Pneumonia	45	3	3	3	General	48	9	7	17	General						1	10	
Yor.	8	10	Pneumonia	47	9	0	0	General												4	
R. J.	9	12	Pneumonia	38	14	2	3	General	41	18	7	14	General	55	4	13	13	General	0	5	
H. W.	10	17	Pneumonia	46	22	12	14	General												6	
H. C.	11	12	Pneumonia	53	17	7	7	General	60	9	0	0	General							4	
G. C.	12	8	Pneumonia	47	16	7	3	Milk and farina	50	12	3	8	Milk and farina	58	4	11	11	Milk and farina	0	12	
Sal.	13	24	Pneumonia	49	7	0	0	General	49	19	11	17	General						4	6	
St.	14	8	Pneumonia	55	7	9	14	General												6	
Ca.	15	2½	Pneumonia	51	30	0	3	Milk						54	13	4	14	Milk	2	8	
G. W.	16	6	Pneumonia	63	6	11	11	Milk												2	
Po.	17	4½	Pneumonia	50	13	0	0	Milk	48	10	6	6	Milk						0	6	
Th.	18	12	Pneumonia						59	12	0	4	General	63	7	2	8	General		4	
T. M.	19	18	Empyema	56	11	6	8	General												4	

La.	20	12	Empyema	45	12	8	8	General	53	20	7	19	General						3	5	
Bu.	21	24	Empyema	60	12	10	10	General												2	
Br.	22	14	Tbc.	52	7	0	0	General						52	14	5	21	General	4	12	
L. V.	23	18	Tbc.	35	10	7	12	General	47	18	8	12	General	59	5	11	11	General	4	10	
P. M.	24	15	Tbc.						38	17	7	10	General	48	6	12	23	General	4	6	
E. K.	25	11	Tbc.	45	10	0	0	General						45	5	12	15	General	0	8	
O. D.	26	21	Syphilis	45	24	0	0	General	41	7	0	2	General	43	21	12	26	General		4	
E. S.	27	24	Syphilis	41	24	0	−8	General	33	23	8	21	General						2	10	
Rz.	28	15	Arthritis						53	10	4	15	General						2	4	
Car.	29	8	Cerv. adenitis						47	18	5	17	General	64	3	9	9	General	0	6	
Gi.	30	9	Arthritis						41	9	4	4	General	45	15	11	19	General	0	9	
A. F.	31	1½	? infection	38	20	0	0	Milk	38	13	7	8	Milk	46	13	17	22	Milk	2	9	
S. W.	32	6½	Abscess						43	20	11	18	Milk and farina						7	14	
A. L.	33	26	No infection	42	13	0	2	General						44	11	11	25	General	3	7	Cu alone in preliminary period
G. L.	34	12	Cataract operation	60	10	0	−1	General						59	6	17	17	General			
A. H.	35	9	Operation	41	7	9	3	Milk and farina						53	6	16	16	Milk and farina		10	Given Cu alone
W. P.	36	24	Twin											31	23	10	41	General	3	13	Cu alone 7 days before Fe
L. M.	37	13	Twin											30	24	18	52	General	6	15	
M. M.	38	13	Twin						30	15	14	17	General	47	11	15	28	General	7	20	
S. M.	39	8½												30	20	16	28	General	5	15	
O. D.	40	8	Premature	25	25	0	7	General						32	26	13	30	General	5	10	
J. N.	41	11	Twin						50	31	4	12	General						3	10	
J. N.	42	11	Twin											30	31	9	42	General	7	20	
S. P.	43	10		43	9	0	−4	Milk	39	21	14	18	Milk	57	6	11	11	Milk	2	12	
W. B.	44	18							29	4	11	11	Milk						6	10	In infection on eleventh day of iron therapy

Haemoglobin estimations were made by the Newcomer method, checked at intervals with the oxygen capacity method of van Slyke. In figuring haemoglobin percentage, 100 per cent is equivalent to 14 g. haemoglobin per 100 cc. Reticulocyte percentages were determined in a fresh blood film made on a slide previously prepared with cresyl blue.

In table 1 is contained a summary of the cases studied. The general make up of the table is, I think, clear—the division into three sections corresponding to the three periods as outlined above, and figures to show the initial haemoglobin, gain in haemoglobin in each period and the duration of the period. The reason for the column showing the rise in haemoglobin during the first four days of observation is not so evident. In any individual case it is of course difficult to evaluate the results of treatment, because it is almost never possible to state, without any doubt, that the improvement would not have started in any case at the very time treatment was instituted. This difficulty is usually avoided by making the period of preliminary observation so long that there can be no doubt that equilibrium has been established before treatment is commenced. This is not a practical method in a hospital where beds are in demand. As may be seen from the table, where there was considerable rise in the haemoglobin in the preliminary period following the end of an infection, between 60 and 100 per cent of this rise took place in the first four days of the period. Conversely, where there was little or no rise in haemoglobin in the first four days, the total rise during the preliminary period was insignificant. This fact allows the use of much shorter periods of preliminary observation without the necessity of a statistical treatment.

In the period of treatment with iron alone, it is not so easy to assert that the haemoglobin will not rise eventually merely because it has not begun to rise within four days. This is due partly to the presence of a latent period of very variable duration during which there is little or no rise in haemoglobin following the beginning of iron therapy, partly to irregularity in the response to iron while the haemoglobin is rising. The variability of the latent period was particularly troublesome. In some cases there was none, *i.e.*, the haemoglobin commenced to rise immediately after iron was first administered. The longest period was ten days (P. C., no. 6), but the usual duration was three

to six days. In a few cases it was found impossible to determine a latent period:—in O. D. (no. 26) there was no essential change in haemoglobin for seven days, but after this time copper was given, and the haemoglobin began to rise. In this case the latent period was arbitrarily taken as seven days, and the case considered as one treated with iron and copper together. In the case of H. C. (no. 11) and T. H. (no. 18), both beginning at about 60 per cent of haemoglobin, there was little tendency for the hemoglobin to rise at all. Since in dealing with the haemoglobin rise statistically the effect of iron was

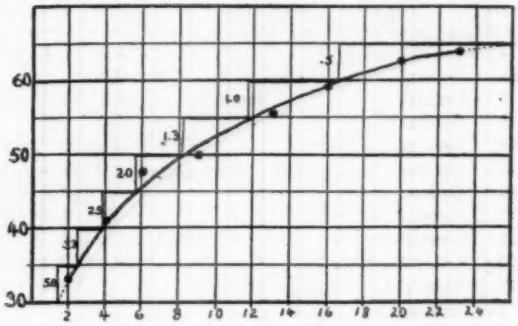

CHART 1. ACTUAL CASE (E. S., No. 27) TO ILLUSTRATE METHOD OF CALCULATING THE SLOPE OF THE HAEMOGLOBIN CURVE DURING EACH FIVE-POINT RISE

The figures beside the curve denote the average rise in haemoglobin per day, *i.e.*, the slope. For the sake of the calculation, the line does not connect the observed points, but has been drawn as a smooth curve. The dotted portion represents extrapolation.

considered to begin at the end of the latent period, these two cases were not included in the statistical treatment.

The irregularity in response to iron while the haemoglobin was rising has been handled statistically. Our method was to construct a curve representing the average rise in haemoglobin on iron alone and to superimpose on this the actual curves observed in the cases treated with iron alone, and with iron and copper. The procedure by which this curve was constructed will next be detailed.

The haemoglobin values in each case were plotted and a smooth

curve constructed between the points. Then the number of days necessary for each five-point rise in haemoglobin was measured off on the base line. From this was calculated the average rise in haemoglobin per day. In this way a series of figures were obtained representing the slope of the curve during successive increments of haemo-

TABLE 2

Measurements of slopes of haemoglobin curves, for each five-point rise in haemoglobin

Each figure represents the average rise in haemoglobin per day during the designated five-point rise.

NAME	NUMBER	DIET	30-35	35-40	40-45	45-50	50-55	55-60	60-65
L. V.	23	General				1.4	1.1	0.6	0.6
M. M.	38	General	4.5	3.5	2.0	0.8			
Ma.	7	General				1.7	1.7	1.7	1.7
J. S.	4	General				1.2	0.8		
Gi.	30	General			1.0	0	0	0	0
E. S.	27	General	5.0	3.3	2.5	2.0	1.3	1.0	0.5
La.	20	General					1.2	0.6	0.6
Sal.	13	General					1.7	1.0	0.4
P. M.	24	General			0.8	0.5	0	0	0
Hol.	2	General				0.6	0.3	0	0
J. N.	41	General					1.0	1.2	0
R. J.	9	General			1.5	1.0	0.6		
Car.	29	General					0.8	0.8	0.6
A. F.	31	Milk			1.3	0	0	0	0
W. Th.	3	Milk and farina				1.7	1.2	1.0	0.8
S. P.	43	Milk and farina			2.5	1.7	1.2	0.3	0
S. W.	32	Milk and farina		2.5	1.7	1.2	0.8	0.8	0
Po.	17	Milk				1.7	1.0	0	0
G. C.	12	Milk and farina					1.0	1.2	0
W. B.	44	Milk	5.0	3.0					
Average			4.8	3.1	1.7	1.1	0.87	0.62	0.4
Days necessary for five-point rise			1.1	1.6	3.0	4.5	5.8	8.1	12.5

globin. An example will make this clear (E. S., (no. 27) chart 1). As may be seen, in this case, the rise from 30 to 35 took place in one day, so that the figure for the slope of the curve between these two points is 5. A day and a half was required for the rise from 35 to 40; the slope is, therefore, 3.3. The slope of the next five-point rise is

2.5, and so on. The same method was applied to all the available cases, and the results are contained in table 2. The figures representing the slope at the same level of haemoglobin in the different cases were then averaged. In a number of cases the haemoglobin tended to remain constant at 50, 55 or 60 per cent for some time. In such

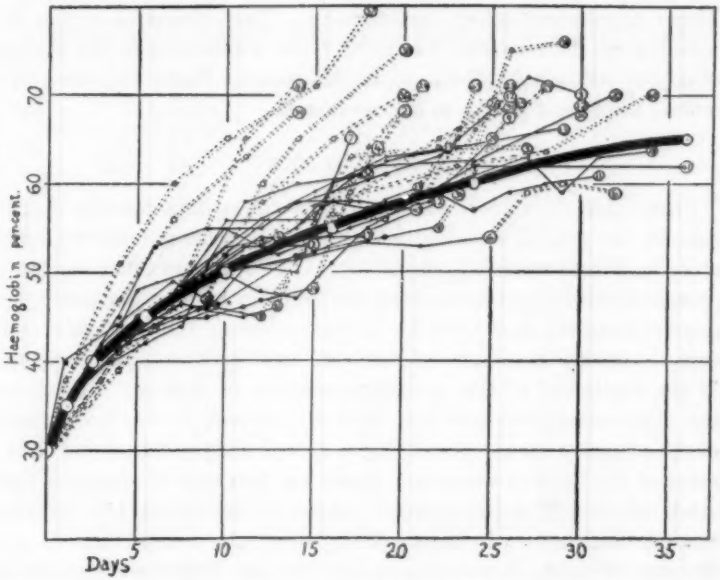

CHART 2. CURVE OF AVERAGE HAEMOGLOBIN GAIN AFTER IRON (HEAVY LINE) OVERLAID WITH THE INDIVIDUAL CURVES FROM WHICH IT WAS CONSTRUCTED (LIGHT CONTINUOUS LINES)

The double dotted lines represent cases receiving copper in addition to iron. The curves have been numbered to make it easier to follow them through the intricacies of the chart.

cases the slope was naturally zero for all the haemoglobin increments above the point at which the haemoglobin curve became horizontal. It is quite probable that had sufficient time been allowed, the haemoglobin would have slowly risen, but the error introduced by not taking this possibility into account is not of any very great importance.

From the average slope it was a simple matter to calculate the number of days required for the corresponding 5-point rise in haemoglobin, and so to construct the curve. This curve is shown in chart 2 as the heavy line.[2] It has been overlaid with the actual curves from which it was constructed. These curves have been numbered for purposes of identification. The double dotted lines represent the effect of copper supplement on the haemoglobin. The success of copper in speeding up the recovery is evident. The mechanism of the action of copper will not be discussed in this paper. There are, however, several important points to be considered.

1. EFFECT OF DIET

From table 1 it may be seen that there was no demonstrable difference in the rate of recovery between those children receiving milk alone and those receiving general diets. This is so whether one compares individual cases in the same age group or whether one treats the cases statistically as in table 2. It is even clearer that vegetables and eggs are inferior as a source of iron to at least ferric ammonium citrate in the treatment of the secondary anaemia of infancy. Certainly, the observations reported here lend no support to the hypothesis of the necessity for the pyrrol ring or special amino acids in the treatment of this type of anaemia. As for the necessity of vitamins, this study offers little for discussion. Many of the babies had rickets, but the fluctuations in haemoglobin were quite independent of the rickets. Vitamin D was included in the diet either as viosterol or cod-liver oil as a matter of course. There was no evidence of scurvy in any of the infants in this series. There was likewise no gross evidence of vitamin B deficiency, but if vitamin B was deficient, it was at least as deficient during the recovery of the haemoglobin as it was during the preliminary period. It must of course be remembered that in the majority of these cases the diet up to the infection that preceded the study was quite adequate.

[2] The curve is identical with the logarithmic curve having the formula $y = 21 \log 10\ x$ in which y = gain in haemoglobin above 30 per cent and x = the elapsed time in days.

2. THE RETICULOCYTE COUNT AND LATENT PERIOD

The latent period was mentioned above, in discussing table 1, as a period that followed the first administration of iron, and lasted a few days, during which there was little visible effect of the iron therapy on the haemoglobin. Actually in many cases the haemoglobin rose slowly from the time iron was commenced, then, after the few days designated as the latent period were over, there was a sharp break and

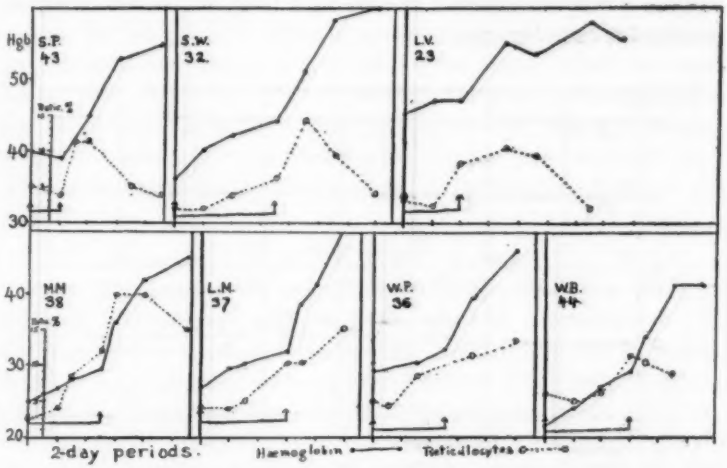

CHART 3. SHOWING THE LATENT PERIOD IN A FEW CASES AND RELATION OF THE RISE IN HAEMOGLOBIN TO THE RETICULOCYTES

The latent period is marked off by the vertical arrows, the first arrow marking the point at which iron therapy was begun. The solid line represents haemoglobin percentage, the broken line the reticulocyte percentage.

the haemoglobin rose rapidly more or less along the curve of chart 2. A study of the reticulocytes gives some insight into the latent period.

As is well known, when iron is given, there occurs a rise in reticulocytes. Certain facts with regard to this rise may be noted.

1. The rise in reticulocytes was not coincident with the rise in haemoglobin, but began almost immediately after iron was first administered, and in many cases the end of the latent period seemed to

be determined by the rise in reticulocytes. This is shown in chart 3 in a few cases. The relationship was striking and common, so much so in cases in which the haemoglobin was initially below 50 that one can make the generalization that the rise in haemoglobin in such cases is determined by a sufficient rise in reticulocytes.

2. The maximum rise in reticulocytes bore a rough inverse relationship to the initial haemoglobin as may be seen from chart 4. This relationship seems to be quite analogous to that shown by Minot to exist in pernicious anaemia treated with liver, but is not nearly so predictable as in his cases.

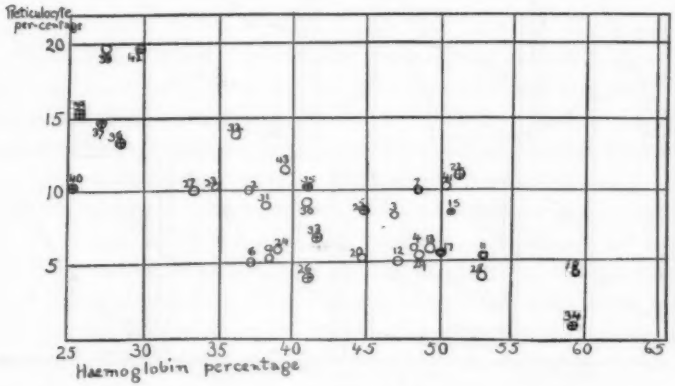

CHART 4. RELATION BETWEEN MAXIMUM RETICULOCYTE RESPONSE TO ADMINISTRATION OF IRON AND HAEMOGLOBIN PERCENTAGE AT THE TIME IRON WAS STARTED

3. Although the end of the latent period and rise in haemoglobin was determined in the majority of cases by the rise in reticulocytes, the attempt to correlate statistically the rise in reticulocytes with the success of therapy was disappointing. Cases for comparison must be chosen from the same age group, they must have the same initial haemoglobin, and naturally must receive the same treatment. It is manifestly impossible to do more with a series no larger than ours than to compare individual cases. This can be done, and it can be shown that there does actually exist a certain amount of correlation,

although the exceptions are numerous enough to make it quite certain that some factor has not been taken into account. From studies recently undertaken this factor is probably connected with the rate of blood destruction.

4. When copper was given after the haemoglobin had begun to rise as a result of the administration of iron, its accelerating effect was immediate and there was no latent period or at most one of a day's duration. When given at the same time as the iron, it had no effect on the duration of the latent period. In three cases copper was given alone. In two it had no effect whatsoever on haemoglobin or reticulocytes until iron was given and the regular latent period was over. In one case, H. O. (no. 35), the haemoglobin rose after copper alone but there was a spontaneous rise in reticulocytes before the copper was given, and it is quite possible that the haemoglobin might have risen spontaneously. Copper had no demonstrable effect on the reticulocytes.

DISCUSSION

From these studies, we may divide blood formation into two functions: 1. Haemopoietic activity as measured by a reticulocyte rise; 2. Haemoglobin synthesis. Unless the bone marrow can be stimulated, it is evident that we have an aplastic condition and cannot expect a rise in haemoglobin. This is borne out to a certain extent by the relation between the rise in reticulocytes and gain in hemoglobin, but the reticulocyte rise, as was mentioned above, is not the only factor of which account must be taken. The factor of blood destruction must be included in any study that is to be considered complete, and investigation along this line promises to throw light on the mechanism of the recovery. (The results of this investigation will be reported in the near future.) The first effect of medicinal iron is to stimulate haemopoietic activity, and unless it does this, there is little chance that a rise in haemoglobin will follow. There is no evidence that food-iron has any effect on haemopoietic activity, though one must be on one's guard at present against concluding that stimulation of haemopoietic activity does not occur merely because there is no reticulocytic response. Such a conclusion may be correct and the evidence seems to support it, but the proof of a negative proposition is a slow process, and at best amounts to little more than "I have never

seen it happen." There is likewise no evidence that copper stimulates haemopoietic activity.

It is futile to discuss whether medicinal iron takes part directly in the formation of haemoglobin, until we have some way of knowing whether in any given case there is or is not an available store of iron in the tissues to be drawn on for haemoglobin formation. We are rather prone to take these stores for granted, forgetting that the belief in their presence is an inference based on somewhat meagre evidence. We know too little about the retention of the iron of the food, especially at a time when there is need for rapid formation of haemoglobin. There is one important conclusion to be drawn—that medicinal iron was far superior to food iron in the treatment of these cases. It is, however, evident that for a maximum rise in haemoglobin some factor is needed in addition to iron even when the haemopoietic tissue has been well stimulated, and that in most cases this factor is not sufficiently supplied by the food, but is supplied by copper. This appears to be the only point at which copper acts, and its usefulness is, therefore, limited to those cases in which there is primarily a deficient formation of haemoglobin, the so-called "hypochromic" anaemias.

SUMMARY

A series of anaemic infants were treated with iron, and iron with copper supplement. The results were considered statistically through the construction of a curve corresponding to the average rise in haemoglobin after iron alone. It was found that copper accelerated the rise in haemoglobin when given in addition to iron. This acceleration was most evident when the haemoglobin was above about 50 per cent, for above this point the haemoglobin curves from cases on iron alone tended somewhat to flatten out, whereas those from cases on iron and copper continued to rise steeply up to about 70 per cent. In this series it made no difference in the speed of recovery whether the child was on a diet of milk alone or whether vegetables or eggs were included, and medicinal iron was found to be far superior to food-iron in causing a rapid recovery. The effect of the iron is first on the reticulocytes, then on the haemoglobin, and there usually exists a latent period before the effect on the haemoglobin is manifested by a rise. The end of the latent period appears to coincide with a sufficient rise in reticulocytes. Copper appears to accelerate haemoglobin formation, and has no effect on the reticulocytes.

THE CIRCULATION OF THE AQUEOUS[1]

JONAS S. FRIEDENWALD, M.D., AND H. F. PIERCE, PH.D.

From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Medical School

PRELIMINARY REPORT

The problem of the circulation of the aqueous, the source, volume of flow, and mode of reabsorption of the fluid has, for years, been recognized as the key to the understanding of glaucoma. In spite of the enormous amount of research which has been done upon this problem, substantial agreement by various investigators has not been achieved. The work which we are reporting was begun eight years ago, and has been continued, with interruptions, since the outset, but with increasing intensity during the past year. Detailed report of these experiments will be published in a series of papers elsewhere. It has seemed worth while, however, to present here a brief outline of the whole investigation so that the relation of its various parts, which may be lost from view in the more detailed discussion, may here be pointed out. We wish to acknowledge the valuable advice which we have received in relation to this study from Dr. Arthur Grollman, Dr. W. Mansfield Clark, and, particularly, from Dr. W. Perlzweig.

The general problem readily falls into three major subdivisions: (1) What, if any, is the volume of flow of the aqueous? (2) Where, and by what mechanism is the aqueous formed? (3) Where, and by what mechanism is it reabsorbed? In regard to the first question three widely differing attitudes are held at present: (a) The followers of the Leber school, among whom Seidel (1) has, in recent years, been the most active, maintain that there exists a continuous, through-and-through, circulation of aqueous. This theory is supported by a great volume of experimental evidence on the course taken by foreign substances, both diffusible and particulate, when introduced into the eye; and by a great volume of clinical evidence on the pathology and

[1] Read in part before the American Ophthalmological Society, June 1, 1931.

pathological physiology of the obstructive types of glaucoma. (b) By a second group of investigators precisely the opposite opinion is held. Based upon chemical studies which showed that the constitution of the aqueous closely corresponds to that of a dialysate or ultrafiltrate of the blood plasma, and upon experimental studies on the mode of appearance in the aqueous of foreign substances, such as fluorescine, when injected into the blood stream, these writers have concluded that the aqueous is in osmotic and hydrostatic equilibrium with the capillary blood within the iris, ciliary body and retina; and that, while an osmotic exchange across the capillary wall is continually taking place, no through-and-through circulation exists. The chief exponents of this view in recent years have been Hertel (2) and his coworkers, also Hamburger (3) and Magitot (4). (c) An intermediate viewpoint is taken by those who believe that, while an osmotic exchange exists throughout the intraocular vascular system, the highest pressure head is probably to be found in the ciliary capillaries, while the lowest pressure head is in the canal of Schlemm, resulting in a small through-and-through circulation of fluid. This view which we hold has, hitherto, been tacitly assumed by many writers, but has been most clearly stated by Wessely (5).

RATE OF FORMATION OF THE AQUEOUS

The volume of flow of the aqueous has been estimated by various workers as from 0 to 50 cu.mm. per minute. These values, however, have all been based on experiments in which either the intraocular pressure or the blood pressure was seriously disturbed. Since the rate of flow can readily be shown to vary considerably with any change in the intraocular or vascular pressure, these results cannot be considered valid. In order to avoid this objection, the following procedure was adopted (Fig. 1). Two cannulas were introduced into the anterior chamber of a dog's eye, one connected with a reservoir of physiological salt solution in such a way that the intraocular pressure was not disturbed. Without changing the intraocular pressure, the anterior chamber could then be filled with a colloid solution by which the normal outflow channels could be clogged up. The most effective agent for this purpose was found to be the animal's own serum. Having blocked these normal outflow channels, any subsequent formation of aqueous

was allowed to escape from the eye through one of the cannulas, without altering the intraocular pressure, and its volume was measured by the movement of a bubble in a capillary tube as shown in the figure. These experiments revealed a rate of flow of approximately one cubic millimeter per minute.[2]

This result was confirmed in a human case by an accidental observation as follows. The patient was a child with a very mild congenital glaucoma which, after the use of myotics for some years, had become compensated, and maintained a normal intraocular pressure without medication, and without loss of vision, for some time. As an additional anomaly, the lenses were extremely small, measuring only 7.0 millimeters in equatorial diameter. Eventually the lens became dislocated in one eye, first into the vitreous, and then into the anterior chamber. Here it bobbed around, like a drop of oil, without causing the slightest congestion of the eyeball or change in the intraocular pressure. In this condition the child was admitted to the hospital for study prior to an attempt to remove the offending lens.

It was the good fortune of one of us (J. S. F.) to see this child one day at noon and to observe that the condition had not changed. Within fifteen minutes the nurse observed that something peculiar had happened. On re-examination it was found that the lens had slipped up over the pupil, and was forming a sort of ball valve with the iris. During the next half-hour the iris slowly bulged forward around the edge of the lens and the anterior chamber became evacuated, but it was not until the iris had approached close to the cornea that the intraocular tension began to rise. It was possible, subsequently, to measure the volume of the anterior chamber in the opposite eye by determining the diameter and curvature of the cornea and estimating its depth with the corneal microscope and an attached scale. Likewise, the offending lens was subsequently obtained for measurement. The difference between these two values gives the

[2] Control experiments showed that the outflow channels were, in fact, blocked almost completely by this procedure, and evidence was also found to show that in these experiments no abnormal formation of aqueous by the iris was taking place, and that, therefore, the rate measured was actually that of the normal through-and-through circulation. Detailed discussions of these controls will be found in the full report.

volume of aqueous trapped in the anterior chamber. This amount of aqueous disappeared from the eye in from thirty to forty-five minutes. From this we could estimate the rate of flow, which was found to be approximately 1.5 cu. mm. per minute, in close agreement with the results obtained in experimental animals.

THE SOURCE OF THE AQUEOUS

What we have measured in this case, and in the previously reported experiment, is a through-and-through circulation from posterior to anterior chamber. The source of this fluid must, therefore, be either the ciliary body or the retina. The latter we can immediately eliminate from discussion, for there is no change in intraocular pressure following embolism of the central retinal artery. It became of interest, therefore, to study the characteristics of the barrier which, in the ciliary body, separates the body plasma from the aqueous. It must be remembered that proof of the existence of a definite through-and-through circulation is in no way a denial of the existence of to-and-fro osmotic exchange between the capillary blood and the intraocular fluid throughout the eye.

Since we have shown that the aqueous is, at least in major portion, formed by the ciliary processes, and since the chemical composition of the aqueous clearly shows it to be derived from the blood, one might assume that the blood-aqueous barrier in this region is permeable to all of the substances found in the aqueous or, more generally, to water and all diffusible constituents of the blood. The problem, however, merits more detailed analysis.

The familiar Ehrlich experiment with the intravenous injection of fluorescine or other acid dye, demonstrates that the barrier is permeable to negatively charged dyes provided the colloidal particles are not too large (*e.g.*, Congo red). In contrast to these experiments various workers have found that basic dyes, such as methylene blue, injected into the blood stream, do not appear in the aqueous. One cannot conclude from this fact that the barrier is impermeable to these substances, for they are very strongly adsorbed by the tissue proteins and probably do not reach the ciliary epithelium in diffusible form. In order to test this matter directly, we injected a solution of methylene blue into the ciliary body of an albino rabbit and found that

the dye appeared in the posterior chamber almost immediately. The blood-aqueous barrier in the posterior chamber is, therefore, freely permeable to water and dissolved substances passing in the direction from blood to aqueous.

When the permeability of the ciliary epithelium for substances passing in the contrary direction, namely, from the posterior chamber into the ciliary capillaries, is investigated, an entirely different result is obtained. Neither water, nor electrolytes, nor dyes have as yet been found to permeate the barrier in this direction.

The experiment to test the permeability for water was performed as follows. Under general anaesthesia a cannula was inserted into the anterior chamber of a dog's eye and was connected with a reservoir of physiological salt solution raised to a level of twice the normal intraocular pressure. A narrow beam of light was arranged to pass down the optical axis of the eye, and a camera, placed at 45° to this axis, was used to photograph the optical section of the cornea and lens produced by the beam. In this way changes in depth of the anterior chamber of as little as 0.05 mm. could be recorded. If, under these circumstances, a small amount of vitreous is withdrawn, then the anterior chamber will be seen to increase in depth, for the iris and lens act as a ball valve in relation to the passage of fluid from the anterior to the posterior chamber. If, therefore, at the high pressure which we used in this experiment, any absorption of fluid should take place through the ciliary body or retina, then a deepening of the anterior chamber would be observed. No change in depth of the anterior chamber was found even after continuous application of twice the normal intraocular pressure for a period of two hours.

It may be thought that some small amounts of fluid might diffuse backward through the iris or pupil without displacing the lens. This possibility was controlled by adding potassium ferrocyanide and iron ammonium citrate to the injected solution in some cases. After injecting these substances into the anterior chamber at twice the normal intraocular pressure for two hours, the eyes were removed and fixed in acid formalin. The anterior chamber, cornea, iris, and pupillary zone of the lens were found to be heavily stained with Prussian blue, but only the faintest traces of this substance were found in the posterior chamber.

In order to test the permeability of the barrier to anions, a solution of potassium ferrocyanide and iron ammonium citrate, isotonic with physiological salt solution, and also one five times as concentrated, were injected into the vitreous of albino rabbits' eyes at pressures of 10 cm. and 30 cm. water above the normal intraocular pressure, for periods of one hour. At the end of this period the eyes were enucleated and fixed in acid formalin. This procedure results in the precipitation of Prussian blue wherever the iron salts have permeated. It was found that the retina, the iris, the lens, Schlemm's canal and the veins connected with it contained the stain, but the ciliary processes including their epithelium showed no penetration of the iron. Similar experiments were performed in which methylene blue was injected in saturated solution into the vitreous at supra-normal pressure for one hour. The eyes were then removed and fixed in saturated bichlorid solution, with which the methylene blue forms an insoluble compound. This method enables one not only to find what tissues the methylene blue reached in its diffusion, but also to distinguish between the oxidized and reduced forms of methylene blue in the tissues, for the former makes a purple compound with bichlorid, the latter a blue one. In these experiments the retina, lens, iris, and cornea, Schlemm's canal, and its connecting veins, were found stained with the dye, while the ciliary body, including its epithelium, was uncolored.

DISCUSSION

Such irreversible permeability as we have found is not an isolated and unknown phenomenon. Fischer (6) has demonstrated that the cornea is permeable to water and anions in the direction from outside, toward the anterior chamber, but is not permeable to these substances in the reverse direction. A voluminous literature exists on the irreversible permeability of the frog's skin. Somewhat similar instances of anomalous osmosis, in which water diffuses through a membrane from a more concentrated to the more dilute solution, have been studied *in vitro* by Jacques Loeb and others. Physical theory would require, in order that these phenomena should take place, that the amount of potential energy on the two sides of the membrane must be unequal. Just what forms the energy should take, whether electrical or chemical, is not clear, nor is the mode of operation of this excess of potential energy understood.

In relation to glaucoma, this finding has considerable importance. It must be clear that if the egress of fluid from the anterior chamber is obstructed, then any additional fluid entering the eye will be absorbed with great difficulty. Naturally, a position of equilibrium between the blood pressure in the ciliary capillaries, and the intraocular pressure, will be rapidly reached. This need not of itself lead to any marked rise in the intraocular pressure. If, however, as the result of a slight and transitory rise in venous or arterial pressure, some small additional amount of fluid escapes into the eye, raising the intraocular pressure, then the return of the blood pressure to normal will not be followed immediately by a return of the intraocular pressure to normal.

In summary, then, the aqueous can be regarded as formed, mainly, by the ciliary body. Its chemical constitution would indicate that it is derived from the blood plasma by ultrafiltration through the capillary walls, but its passage across the double layer of epithelium of the ciliary body must be accomplished at the expense of work done by the tissues. If the transfer did not involve the loss of free energy, it would not be irreversible. Whether this is to be considered a secretion depends on the definition of the word. If one defines a secretion as a cellular product which contains some substance not present in the mother liquid, or present in marked excess in comparison with the mother liquid, then the aqueous is not a secretion. If, on the other hand, one defines a secretion as a substance whose formation is the result of work done by the tissues, then the aqueous is a secretion.

THE OUTFLOW

The reabsorption of the aqueous from the anterior chamber has been the subject of many investigations. The part played by the canal of Schlemm has, by some, been considered paramount, by others minimal. According to the older Leber theory, fluid entered Schlemm's canal by filtration through its walls. Seidel has shown that the wall of Schlemm's canal is permeable to water, crystalloids, and highly dispersed colloids, but is impermeable to large colloidal particles, in this respect resembling capillary endothelium elsewhere in the body. Duke-Elder (7) has shown that the hydrostatic pressure in the canal exceeds that in the anterior chamber by a small amount. Since fluid cannot filter from the low to the high pressure side of a

membrane, he has suggested that the reabsorption of the aqueous is the result of osmotic forces due to the presence of plasma proteins within the lumen of the canal. (Duke-Elder regards the part played by Schlemm's canal in the re sorption of aqueous as relatively unimportant.)

Ridley (8) and others have objected to this hypothesis because, on histological section, the canal of Schlemm generally is not found to

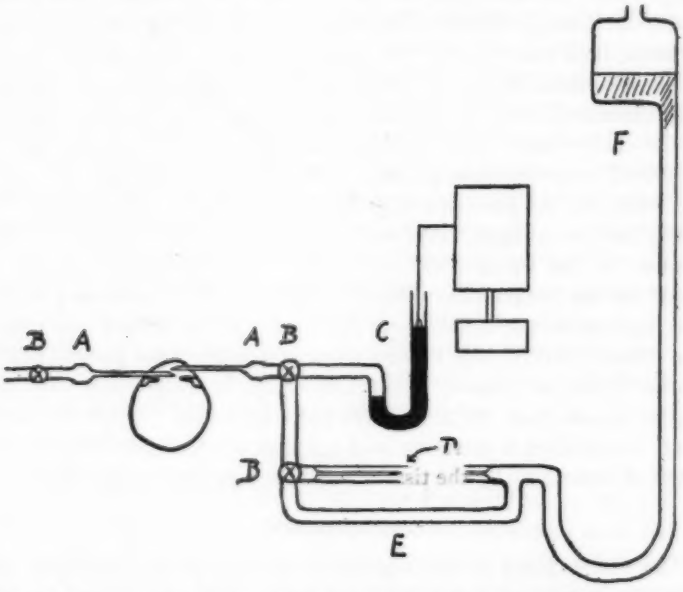

FIG. 1. *a*, cannulas in anterior chamber; *b*, stop-cocks; *c*, mercury barometer and kymograph; *d*, capillary tube with air bubble; *e*, wide-bore tubing; *f*, movable salt solution reservoir.

contain blood. Against this it may be argued: (1) The canal has direct connections with the ciliary veins on the one hand, and the episcleral veins on the other. Unless these two venous beds constantly maintain an equal pressure, a flow of plasma into the canal must occur. (2) When the eyeball is congested, blood may be found in the canal both clinically and on histological examination. (3) The best

available data on the pressure in Schlemm's canal (Duke-Elder) indicates that this exceeds the intraocular pressure by only one or two millimeters of mercury. The osmotic pressure of the plasma proteins is between 25 and 30 mm. Hg. At osmotic equilibrium between the intraocular pressure and the intra-Schlemm's canal pressure, the plasma

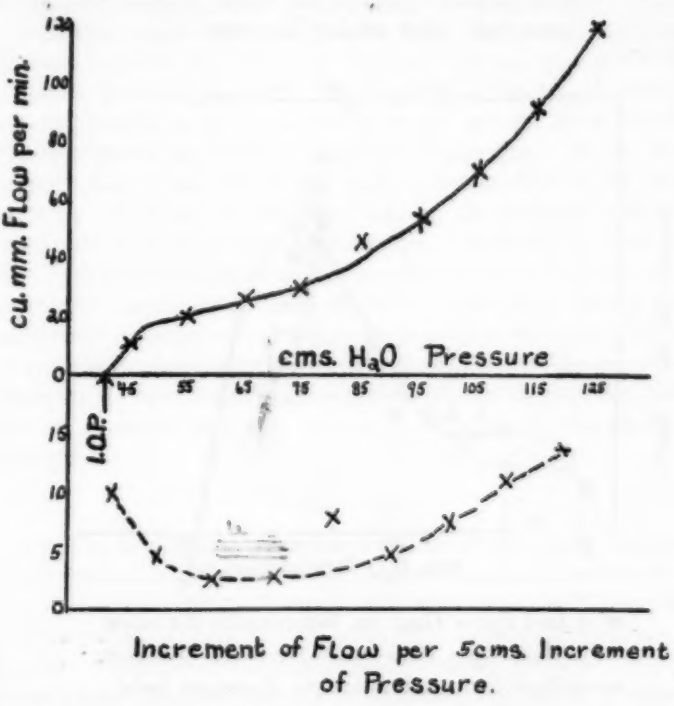

FIG. 2. RATE OF OUTFLOW FROM ANTERIOR CHAMBER AT VARIOUS PRESSURES

within the canal must be diluted by aqueous in a ratio lying between 1:15 and 1:25. Any increase in the concentration of plasma within the canal over this minute amount will be sufficient to initiate a flow of fluid from the anterior chamber into the canal. (4) Finally, when an eye is removed and fixed for histological study, the pressure in the vessels with which Schlemm's canal connects is reduced to zero and

ample opportunity is allowed for this small amount of plasma to be washed out.

In a series of experiments, we measured the rate of flow of fluid into the eye from a reservoir at different levels of pressure. A typical result is shown in figure 2. It will be seen that, as the pressure is

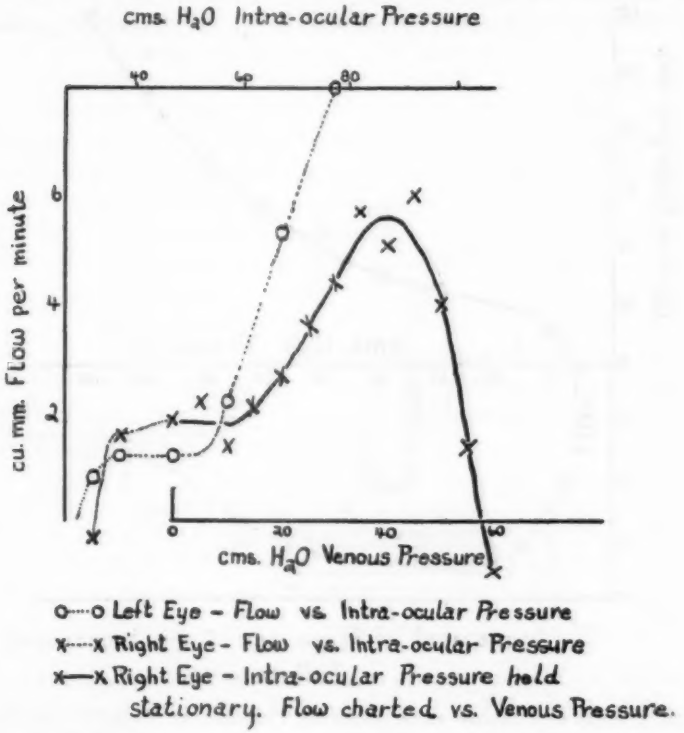

FIG. 3. EFFECT OF VENOUS PRESSURE ON THE RATE OF OUTFLOW FROM ANTERIOR CHAMBER

raised above the normal intraocular level, a considerable flow occurs, and that, with a change of only a few millimeter Hg of pressure, the rate may be 5 to 10 times as great as the normal, determined in the experiments previously reported. At this point, presumably when

the intraocular pressure has equalled the intraocular venous pressure, a further rise in intraocular pressure causes little or no change in the rate of flow of fluid, each small change in intraocular pressure being compensated for by a corresponding rise in intraocular venous pressure. This plateau, in our curve, reaches up to the level of mean arterial blood pressure, where another sharp break is found.

Schlemm's canal which lies farthest down in the vascular pressure gradient must be the first to be collapsed by the application of increased intraocular pressure. By compressing the jugular veins, the venous pressure in the head can be raised and the canal reopened. Figure 3 shows the result of such an experiment. As the venous pressure is increased, the rate of reabsorption of fluid out of the eye increases. This can be explained only on the assumption that the canal absorbs fluid by osmotic attraction. Similarly, we have found that a rise in arterial pressure, if accompanied by a sufficiently marked peripheral vasodilatation, may result in a fall rather than a rise in intraocular pressure. In this case the peripheral vasodilatation must be associated with a more rapid flow of plasma into the canal, compensating by its increased osmotic attraction for the increased formation of aqueous normally associated with an increased arterial pressure.

DISCUSSION

It will be seen from these experiments that the circulatory dynamics of Schlemm's canal, and its connecting venules, is measurably dissociable from that of the intraocular capillaries, and, in fact, is precisely so arranged as to check any gross change in intraocular pressure produced by changes in the general arterial or venous pressure. We have shown above that the presence of proteins in the anterior chamber diminishes the rate of outflow of the aqueous. On the other hand, we find that congestion and vasodilatation increase the rate of outflow. In many cases of intraocular inflammatory disease, the intraocular pressure may be largely determined by the balance between these two conflicting forces.

The conclusions which we have drawn from this series of experiments in regard to the circulation of the aqueous do not in any way conflict with the well established facts regarding the chemical con-

stitution of the aqueous. Chemically, the aqueous approximates the constitution of a dialysate of the blood plasma. It tends, as Duke-Elder and others have shown, toward thermodynamic equilibrium with the blood. In the main, the barrier between the blood and the aqueous must behave as an inert semipermeable membrane; or when, as in the ciliary epithelium, the barrier is an active one, its activity must be such as to affect all the constituents of the aqueous equally. This is sufficient to prove that the source of the free energy in the ciliary epithelium is not in a difference in the electrical charge on the two surfaces, for such electrical differences would affect oppositely charged ions oppositely, and would alter the chemical composition of the aqueous from that of a dialysate. These conditions of thermodynamic equilibrium, however, in no way require hydrostatic equilibrium. Chemically, one could not distinguish between an equilibrium reached by dialysis, and one approximately by combined ultrafiltration and osmotic reabsorption.

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